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Foreword

Heart disease is now the greatest public health problem on this continent. The leading cause of death, it takes a toll greater than the next five leading causes of death combined. In addition, the social and economic loss due to illness and chronic disability is very large. All ages and both sexes are affected, but particularly middle-aged men at or near the period of their greatest value to their families and to society.

Recent years have seen gratifying and sometimes spectacular advances in the diagnosis and treatment of cardiovascular diseases. A few, such as syphilitic aortitis and diphtheritic myocarditis have almost disappeared. Others, such as thyrotoxic heart disease and subacute bacterial endocarditis, once common, are now rather rare. Improved understanding of psychosomatic symptoms and of the significance of many systolic murmurs has reduced unwarranted cardiac invalidism. Prophylactic penicillin has reduced the incidence of rheumatic fever. Surgery of the heart and great vessels has cured many patients and greatly benefited many more. Rehabilitation measures have returned many cardiac patients to a useful and rewarding life.

Despite this progress much remains to be done. The causative mechanisms of the still-unconquered major cardiovascular diseases of atherosclerosis, hypertension, rheumatic fever, and congenital heart disease are incompletely understood. Yet enough is known to suggest that at least some of the problems involved are capable of solution, perhaps quite soon. What is needed is fundamental research to provide new knowledge of the cause and prevention of these diseases, and full application of the already available knowledge to patients suffering from these diseases.

To further these needs, the Canadian Heart Association was formed in 1946 and the National Heart Foundation a decade later. This special issue of the Manitoba Medical Review opens with accounts of the origin, objectives, and accomplishments of these organizations. In these days, when the medical profession is often unfairly criticized, it may not be inappropriate to indicate that this concerted attack on heart disease was initially conceived and inspired by doctors — though its eventual success must depend on widespread and sustained public assistance. This month the Heart Foundations of Canada are again seeking this support.

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History of the Canadian Heart Association*

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Before the early 1920's there were no societies of heart specialists. The earliest ripples of movement which led to the creation of the American Heart Association occurred in New York City in the year 1912. Those men who heralded the formation of the Cardiac Society of Great Britain and Ireland could be noticed in London in 1920. In Canada, the earliest signals that a Canadian Heart Association would come into being were flashed, very weakly, in 1926. In 1912, Dr. Hubert V. Guile and his social service assistants studied the rehabilitation of cardiac patients. This pointed up the need for more of similar work. In the same year Dr. Lewis A. Conner, who later became the first president of the American Heart Association and the first editor of the American Heart Journal, organized a trade school for cardiac convalescents known as the Sharon Shop, with the object of promoting the rehabilitation of these patients. In relating the story of the early beginnings of organization among cardiologists in England, Dr. John Cowan[1] makes this observation. "Before the First World War, Sir James MacKenzie had suggested to a few friends who were interested in heart disease that such an organization should be made. And so the Cardiac Club, which was formed after the war, really was conceived in Burnley where Sir James MacKenzie began his notable career." Dr. Cowan then speaks of the war as follows: "Another European war came and our profession was scattered over the world. It was not a great war for it altered little save garden fences, but it left a terrible swathe behind it. Many men had died and many more were suffering in health from wounds or sickness for whom provision was required. During the war the pension service was necessarily a makeshift; the staff was insufficient and inexperienced and their decisions needed revision and co-ordination. Many cases were cardiac, at least in name. And so in April, 1920, the Ministry appointed consultants to aid the regional directors in the assessment and treatment of the cardiac patients. The marked majority of those appointed had been associated with James MacKenzie before the war." This group of consultants gradually became aware of the fact that they could have very profitable times discussing medical subjects formally among themselves. They therefore organized what they called the "Cardiac Club," with James MacKenzie as their first and only honorary member. This happened in 1922. In New York City, the work of Guile and of Lewis Conner gradually became extended so that others took part in it, and by 1923 a very active movement was initiated, which led to the eventual creation of the American Heart Association as a national body to which members of the profession who were especially interested in heart disease could belong. The principal objects of this Association were the prevention and relief of cardiovascular disease. Among the men in New York City who had much to do with encouraging the formation of this Association was the late Dr. Haven Emerson. I know a story about his contribution which, whether apocryphal or real, is relevant. He estimated, in 1912 or thereabouts, that the twentieth century would see the abolition of the infectious diseases, including tuberculosis, and that, once this happened, the major public health problems would be related to cardiovascular and malignant diseases. His prophetic views have almost been realized now at mid-century. It was in the light of the fact that for all the infectious diseases, techniques for the prevention of disease were discovered long before techniques for their cure, that the main objectives of the American Heart Association were stated as the prevention and relief, rather than the cure and prevention. Prevention and relief are the truly practical ideals. Typhoid fever could be prevented by hygienic measures and immunizing vaccine, for sixty years before a drug was discovered that would cure typhoid fever in the person afflicted by it. It is to be hoped that the same may be achieved in the domain of heart disease, namely, that we will learn to prevent heart disease even before we learn how to cure it. The American Heart Association was formally organized on June 10, 1924.

The year 1925-1926 saw the return to Montreal of three young men who had graduated in 1920, Albert de Guise, from the University of Montreal, Ray Brow and Harold Segall, from McGill. We had each spent the intervening five or six years in training for a career in cardiology. Dr. Cecil Birchard, who had had some experience working with Sir Thomas Lewis during World War I, had pioneered the introduction of electrocardiography at the Montreal General Hospital. One day in the summer of 1926 we four had a luncheon meeting to explore the possibility of organizing a Canadian Heart Association analogous to the American Heart Association. We had a good luncheon, but we did not undertake to organize the Heart Association. Perhaps, this disappointed me to a greeater degree than necessary, because it might have been unwise to begin at a time when so few men in Canada would have been interested. Very soon afterwards, the depression and World War II consumed years during which one did not start new organizations of this kind. By 1946 many cardiologists were active in our country, and the notion that there should be a

*Address delivered at the annual meeting of the Heart Foundation of Canada, June 4, 1959, at Montreal.

Canadian Heart Association probably occurred to more than a few. The spark that initiated the required action came suddenly one evening in February of 1946.

A few days earlier, Dr. Wilder Penfield had told some of us that Montreal was being visited by a distinguished cardiologist from Mexico, Dr. Ignacio Chavez, who had come to visit his son, a student at the Neurological Institute. We arranged some professional and social events for him. Thus on that evening in February, 1946, Birchard, Brow, Hebbel Hoff, who was then professor of physiology at McGill, and I gave a dinner in honour of Chavez. A very pleasant stream of conversation, coloured strongly by Birchard's opinions on many things including the Gold Standard, flowed throughout the meal. Dr. Chavez spoke little—he seemed to fit the definition of a fine conversationalist. Then at the coffee and brandy stage he suddenly interrupted our light hearted mood by making what seemed a quite formal, apparently prepared speech. He announced officially, that in October, 1946, the second inter-American Congress of Cardiology was to be held in Mexico City; he urged that a Canadian Heart Association should be formed so that it could send a delegate. The business of the luncheon of 1926 was now resumed, but this time success crowned the efforts of this nucleus of four. At a meeting called by Professor Hoff on September 25, 1946, fifteen interested men assembled. They formed the Montreal Cardiac Society and planned the creation of the Canadian Heart Association. John Palmer undertook to corral the cardiologists who would be present at the meeting at the Royal College in Ottawa in November, and I volunteered to attend the Congress in Mexico City as a semi-official delegate.

On November 16, 1946, Palmer brought together in Ottawa eleven cardiologists who represented the length and breadth of Canada. At this meeting, formal decisions were taken and recorded in official minutes by Birchard. Item (a), the first resolution, was, "That the establishment of a national heart association is feasible and desirable." We aimed to achieve this objective in June, 1947, in Winnipeg, at the time of the annual Canadian Medical Association meeting. A committee of the Montreal group consisting of Hoff as chairman, Segall as secretary, John Palmer and Rodrigue Lefebvre were charged with the task of organizing the details. The secretary of this committee went to Winnipeg armed with a draft of the constitution. The ground had been prepared by letters sent to all the men in Canada who had a special interest in cardiology, and the organization meetings under the chairmanship of John McEachern consummated the creation of the Canadian Heart Association on June 24, 1947. George Strong, Francis Mathewson and David Baltzan were towers of strength in easing the birth pangs; they assisted in performing some effective plastic surgery on the draft of the constitution. It was Dr. G. E. Hall, now president of the University of Western Ontario, who moved, "That a Canadian Heart Association be organized." In due course on that day the following officers were elected as recommended by the nominating committee.

President ..... Dr. Cecil C. Birchard
Vice-President ..... Dr. John McEachern
Secretary-Treasurer ..... Dr. Harold N. Segall

Members of Council

Dr. John Scott, Edmonton
Dr. Kenneth A. MacKenzie, Halifax
Dr. George E. Hall, London
Dr. Hebbel Hoff, Montreal
Dr. Rodrigue Lefebvre, Montreal
Dr. David Baltzan, Saskatoon
Dr. John Keith, Toronto
Dr. John Hepburn, Toronto
Dr. George Strong, Vancouver
Dr. Francis A. Mathewson, Winnipeg.

After the business session was completed, the first scientific meeting took over. The programme consisted of one item. Palmer had arranged for a lecture by Dr. John McMichael, of London, England, who was visiting Canada as a guest of the Canadian Medical Association. Dr. McMichael spoke for about forty-five minutes on "Some Aspects of the Circulation in Arterio-Venous Aneurysm." The meeting was attended by about thirty men and altogether was an exhilarating experience, not unlike that felt by a father at the birth of a much wanted child.

In the years from 1922 to 1946 the activities of the American Heart Association consisted mainly in holding annual scientific meetings and in publishing the official journal, The American Heart Journal. The annual meeting varied in size, but I cannot recall any one that was attended by more than 200 people. At the last meeting of the American Heart Association in 1958, 2,000 people registered. This is an obvious indication of the growth of interest in problems of cardiovascular disease by members of the medical profession, and the increasing numbers of men who have become highly expert in dealing with these problems. In 1946 when it was twenty-three years old the American Heart Association re-organized with the object of making a partnership between the doctors and the general public in fighting the ravages of heart disease. The Canadian Heart Association had a similar career, but only for about half the total time. Thus, between 1946 and 1956, while the annual meetings were of the usual scientific nature and grew in length and in size, the council meetings were occupied by plans for eventually following the example of the American Heart Association and initiating a public interest in the problems of cardiovascular disease. Naturally there were those who favored and those who opposed this step. The pros hoped for the right moment to come. It did

come, in 1954, when Dr. George F. Strong became the president of our Association, with John Keith as secretary. Keith had been secretary-treasurer since 1951.

George Frederick Strong, usually known as "Fritz" Strong, was born and educated in St. Paul, Minnesota. After four years of post-graduate studies in the East, including Boston, he chose to settle in Vancouver where he had served for part of a year at the Vancouver General Hospital in the early phase of his training. Lucky Vancouver! "Fritz" Strong not only established his place as a leading internist-cardiologist, teacher and contributor to technical advances in our art and science, but he also assumed vigorous leadership in developing and expanding the communal units which served Vancouver in particular and mankind in general. His biography reveals a long list of chairmanships and presidencies. In the years 1954 to 1956 he was president of the Canadian Medical Association, the American College of Physicians and the Canadian Heart Association. During the year 1954-1955 he re-examined the question of whether the Canadian Heart Association should become active in raising funds for research and came to an affirmative conclusion. He summarized these personal deliberations at a meeting of the Association in June, 1955, when he declared, "either the Association should do something about it now, or else stop talking about it." Much had already been done by the team of George Strong and John Keith in the previous year. They had had an interview with Mr. Paul Martin, the Minister of Health and Welfare, who granted his enthusiastic support for the establishment of a National Heart Foundation. From this point onward events moved with planned precision. Mr. Martin invited representatives, both lay and medical, from all parts of Canada to a National Heart Conference, under his auspices in Ottawa. This was followed by an organizational meeting on June 7, 1956, on St. Helen's Island in Montreal, and the National Heart Foundation was established with "Fritz" Strong as its first president and Mr. Albert Deschamps and Mr. Douglas Ambridge as vice-presidents. The last meeting of the Canadian Heart Association, which George Strong attended, took place in Quebec City on June 14th and 15th, 1956. Thus, after two momentous years of great leadership he relinquished the presidency. Our appreciation of his signal services was underlined by a source of strength. The Canadian Heart Association had received a legacy of $10,000.00 from the estate of the late Mr. Frederick Bates, of Chatham, Ontario, in 1951. This sum was offered by the Canadian Heart Association to the National Heart Foundation of Canada as an interest-free loan to help in the early steps of its organization. You may imagine that there was a great deal to do, and that George Strong had a large part in everything that was going on. He had many meetings to attend. And so it came about that he arrived in Montreal, by train, on the evening of February 26, 1957, to attend an executive meeting of the National Heart Foundation on the following day. As he was standing on Osborne Street in front of the C.P.R. station, while a taxi was being hailed by his companion Mr. Ormsby Doherty, he dropped to the ground, struck down by coronary artery disease. "Fritz" Strong died in action, on the front line of our campaign for the prevention of just such tragically premature deaths. He was sixty-two years old.

George Strong remains as a living force among us. The National Heart Foundation exists at present because of his forceful and wise leadership of the Canadian Heart Association.

As might be expected, members of the Canadian Heart Association played leading roles in the organization of the provincial and regional Heart Foundations. Moreover, our highly esteemed Medical Director, Dr. John Armstrong, was recruited from amongst members of the Canadian Heart Association. Dr. John Keith ably continued the task of president of the Foundation and steered it through the first National Heart Fund campaign. Then during the past year Mr. Alex Hill, as president, and Mr. Douglas Ambridge and the late Dr. John Palmer as vice-presidents, have achieved major progress and have laid solid foundations for future development at a rapid pace. Much energy, the product of brains and of money, is needed and is forthcoming. The job will surely be done well —the job to prevent premature death.

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The Heart Foundations of Canada

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The history of the heart movement in Canada resounds with the names of Dr. Harold Segall and the late Dr. Palmer of Montreal. Dr. John Keith and the late Dr. Hepburn of Toronto, Dr. Mathewson of Winnipeg and the late Dr. Strong of Vancouver. Dr. Segall has written elsewhere in this issue of the history of the Canadian Heart Association, of which he was the first secretary-treasurer and a writer of its constitution in 1947. The following year, Dr. Hepburn convened a meeting of Ontario cardiologists to consider the formation of an Ontario heart association. With Dr. Keith as secretary, advice was sought from the Ontario Medical Association. The latter urged that a Section on Cardiology be formed within that Association.

The Section on Cardiology was created and had its first meeting in June 1949. Representations were then made to the Ontario Department of Health regarding the setting up of an organization to assemble information on heart disease and to encourage and advise on applications for research. From these meetings, a project, known as "Cardiac Disease Preventive Service" was approved in 1950 under the National Health Grants (No. 605-9-35) in the amount of $12,325. This project authorized the procurement of a medical director, office space and staff and the purchase of educational material. To supervise these activities, the Section on Cardiology and the Deputy Minister of Health for Ontario, formed the Ontario Committee on Cardiology with Dr. Keith as chairman. A subcommittee on research, which was appointed, recommended approval of an initial research programme of $10,000 for 1951-52. This sum represents the beginning of the research activities, later to be supported by the Heart Foundations of Canada.

It is worthy of note that in the cardiovascular field, the four Federal Government agencies sponsoring medical research, awarded $212,000 in extra-mural grants-in-aid in 1951. By 1959, Heart Foundation support had risen to $457,397, whereas the Federal Government grants were now $907,935.

The story of the Heart Foundations begins in Ontario.

At its Annual Meeting in 1951, Dr. Keith presented a brief to the Section on Cardiology regarding the formation of a Heart Foundation in Ontario with lay and medical members, the lay members to take responsibility in the handling of money, and the physicians to act in an advisory capacity. The Section approved these principles and empowered its executive to prepare and present such a proposal to the Ontario Medical Association and the Provincial Government. The Ontario Heart Foundation was incorporated in the Province of Ontario under the Companies Act on April 4, 1952.

Originally, the Ontario Heart Foundation was a group of doctors, but at its first meeting, its membership was enlarged to include five prominent business men, who were elected to its Board of Directors. The Ontario Committee on Cardiology was dissolved, and the Foundation continued to act on behalf of the Ontario Government with regard to the National Health Grants. It received compensation from the Ontario Government for its administrative expense. During 1953-54, the Ontario Foundation administered sixteen National Health Grants to a total of $88,705. In 1955, the Foundation received its first annual grant for research from the Provincial Government. It was a grant of $100,000 and in 1959 the grant was increased to $150,000.

Coincident with the early heart activities in Ontario, the Officers of the Canadian Heart Association, Drs. Hepburn, Segall and Keith, met with the Deputy Minister of Health in Ottawa, in December 1951, to "discuss the financial needs of heart work across Canada." A budget was proposed whereby the Department of National Health and Welfare was asked to consider the allocation of $300,000 to be placed with $600,000 raised from government and the public throughout the provinces. Little seems to have come from this meeting, though the seed was planted. In 1953, the Canadian Heart Association learned that it was to be the recipient of a legacy of $10,000 to be devoted to cardiovascular research in Canada. It was felt that there was need for guidance in the obtaining and allocating of funds. A guide was prepared by the executive: Drs. Segall, Strong and Keith, and was adopted the following year. Some moment was made of the advantages of private sources of funds, of working with lay persons in fund raising and of the formation of regional societies or foundations.

Through the efforts of Dr. Strong in Vancouver, the British Columbia Heart Foundation was constituted under the Societies' Act in 1955. It held its first campaign for funds in February, 1956, and realized over $15,500. In May of that year, it decided to join the Community Chest of Greater Vancouver. This agreement limited the Foundation's educational and organizational activities to the remainder of the province, and after two years experience with declining Chest receipts, the Foundation has given notice that it wishes to regain its autonomy and withdraw from the Chest.

The Quebec Heart Society, Inc., was created under the Quebec Companies Act on May 24, 1955,

by a group of Jewish ladies in Montreal. Early in 1956, the sum of $12,000 was raised and distributed to hospitals in the area. On March 16, 1956, it became the Quebec Heart Foundation. A new Board of Directors, composed of prominent Montreal business men, was elected and continue to serve. The Saskatchewan Heart Foundation was incorporated under the Companies Act of that province in April 1956.

In 1955, Drs. Strong and Keith had an interview with the Hon. Mr. Paul Martin, Minister of National Health and Welfare, who had agreed to sponsor a meeting, having in mind the establishment of a Canadian Heart Foundation. The Canadian Heart Association then authorized its executive to proceed with all necessary arrangements to bring into being such a Heart Foundation.

A National Conference on Heart Disease was assembled in Ottawa on January 16, 1956, representative of all areas of Canada and of all interests in the subject. The Conference recommended the establishment of a Foundation and appointed a committee under the chairmanship of Dr. R. F. Farquharson of Toronto, to draft aims, constitution and by-laws, to apply for a federal charter, and to plan an organizational meeting for June 7, 1956.

The Organizational Meeting was held on Ste. Helene's Isle at which the Letters Patent of the National Heart Foundation of Canada were read. These were granted on June 1, 1956.

> "to co-ordinate and correlate the efforts of organizations and individuals interested in heart disease with a view to reducing the morbidity and mortality therefrom in Canada."

The by-laws were ratified and Dr. Strong was elected the first President, together with his Officers and Board. Dr. T. C. Routley, then President of the Canadian Medical Association and the British Medical Association, was instrumental in obtaining a grant of $60,000 spread over two years from the Canadian Life Insurance Officers' Association, designated as a "Launching Fund." The Canadian Heart Association made available an interest free loan of $10,000 at its meeting the following week. The author was appointed to take office January 1, 1957, sharing space at this stage with that kindly offered by the Ontario Heart Foundation.

The Alberta Heart Foundation was incorporated in December 1956 and the Manitoba Heart Foundation in May 1957. At its first Annual Meeting in June 1957 in Edmonton, formal affiliation with Provincial Heart Foundations was established and Corporate Membership was granted to those two great friends of the Foundation — The Canadian Heart Association and the Canadian Life Insurance Officers' Association. Each body was given representation on the National Board of Directors in accordance with its by-laws. Dr. Keith was elected President, Dr. Palmer Vice-President, and Dr. Mathewson Chairman of the Medical Advisory Committee.

At this meeting, a statement of Policy was adopted which established the general patterns of activity in research, education, fund raising and organization. It was realized that without more substantial resources, the support of research could not be undertaken. Accordingly, the first nation-wide appeal in the name of the Canadian Heart Fund was carried forward under the capable chairmanship of Mr. James Muir, Chairman and President of the Royal Bank of Canada, in February 1958. Over $600,000 was raised by public subscription, of which $425,000 was devoted to research. This research programme was co-ordinated through a Scientific Subcommittee set up by the National Foundation, which reviewed grant applications from all parts of the country. The Foundation, by means of its educational programme, was represented by exhibits and educational materials at many national meetings.

At its Second Annual Meeting in Toronto in June 1958, Mr. Alex B. Hill was appointed its first lay President. At this time, Divisions of the National Foundation were formed in New Brunswick and Nova Scotia, and contact with interested persons had been established in Newfoundland and Prince Edward Island. The Heart Foundations became truly national. Under the chairmanship of Mr. Neil J. MacKinnon, President of The Canadian Bank of Commerce, the second Canadian Heart Fund campaign was held in February, 1959, much of the campaign material being prepared by the National Foundation. The people of Canada endorsed this campaign, in the amount of $756,139, of which, together with government and other funds administered by the Heart Foundations, $598,864.73 was allocated to specific research projects. In the professional education, symposia, lectures and travelling teaching on cardiovascular disease were supported in many provinces. Reprints and other special publications, such as "Modern Concepts in Cardiovascular Disease" were supplied to many physicians on request.

The Third Annual Meeting was held in June 1959 in conjunction with the Annual scientific sessions of the Canadian Heart Association. This meeting proved most fruitful, not only because of the very high calibre of the papers presented, but also because it permitted the scientists and the business leaders, both devoted to the common purpose of alleviating cardiovascular disease, to meet in informal exchange to their mutual advantage.

During the past few months, the programmes of the National Heart Foundation continued to enlarge. Applications for research support totalling more than $940,000 have been received for review. A more extensive professional education programme has been developed, and a larger programme of education to the public of Canada is being carried through by the use of exhibits, films for school and service club use, and, of course, the distribution of approved pamphlet material on re-

quest. This lay education programme deals with heart attack, strokes, arteriosclerosis, hypertension, and rheumatic fever prevention, not by describing symptoms and signs, but by clarifying these conditions in the light of our limited knowledge, and emphasizing the need for further research. Indeed, the activities of the Heart Foundations—research, professional and lay education — are all forms of preventive medicine. They are in no way involved in individual patient care as a matter of policy. They do not offer the palliative of treatment or welfare organizations, but in the prevention of disease, The Heart Foundations of Canada lead towards their own ultimate elimination.

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Cardiovascular Diseases in Hospitalized Patients

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President of the Canadian Heart Association

Introduction

The Montreal Institute of Cardiology is entirely devoted to the diagnosis and treatment of cardiovascular diseases. Located in the Maisonneuve General Hospital, the Institute is a complete unit by itself and comprises 54 beds, a large outpatient clinic staffed by full time cardiologists and surgeons, an x-ray diagnosis room for routine chest and heart x-ray, heart catheterization, angio and cineangiocardiography, and operating room with three post-operative nursing units, research laboratories, a conference room, a library, a photography unit and its own social service. The Institute constitutes the regular department of cardiology for the General Hospital and has all the facilities for routine laboratory procedures and consultations of that Hospital.

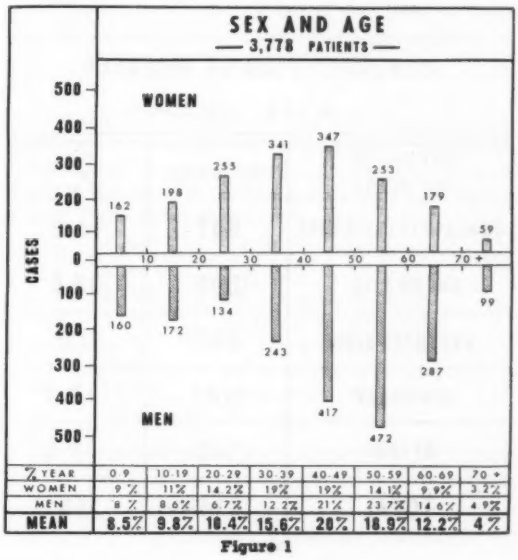
The Institute started its activities in January 1954. After five years of experience, data have been accumulated which may be representative of the incidence, sex, age and distribution of heart diseases at least in the Province of Quebec. In this article, is presented the overall situation of hospitalized patients. Later on, an identical study will deal with the out-patients of the Institute. These studies may shed some useful light for all those interested in stimulating a dynamic program to fight heart diseases which are responsible for the highest morbidity and mortality in our Canadian population.

Material

From January 1st, 1954, to December 31, 1958, 5,028 patients were hospitalized for a total 82,226 days, an average of 16.3 days per patient. Men and women were about equally divided: 2,585 men (51.5%) and 2,443 women (49.5%). This fact demonstrates that heart diseases affect both sexes equally. It will be seen later on that in some forms of heart disease, the sex distribution is not identical and has a definite affinity for one or the other.

Age Distribution

This factor was studied for the first 3,778 well-proven cardiac patients. The findings are summarized in fig. 1.



% YEAR	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70 +
WOMEN	9 %	11%	14.2%	19%	19%	14.1%	9.9%	3.2%
MEN	8 %	8.6%	6.7%	12.2%	21%	23.7%	14.6%	4.9%
MEAN	8.5%	9.8%	10.4%	15.6%	20%	18.9%	12.2%	4 %

Figure 1

It is worth noting that 44.3% of these patients were less than 40 years of age at the time of admission. This fact should be remembered when a too-close association is made between the incidence of heart diseases and physiological aging.

These data may not reflect exactly the true percentage of symptomatic heart diseases in the population at large, but it gives a fair idea of the age of those afflicted with heart diseases seeking medical treatment for their condition. Because of the limited number of beds at the Institute, some priority is given to young patients, especially those for whom surgical treatment may cure or relieve their heart condition.

On the other hand, these figures are large enough to demonstrate the importance of heart diseases in young and middle-aged people.

The peak of hospitalization for heart diseases was between 30 and 50 years in women and 40 to 60 for men.

Diagnosis

These statistical data were limited to the more frequent cardiovascular diseases: congenital, rheumatic, hypertensive and coronary heart diseases. A last group included pericarditis, cor pulmonale and aortic disease. A careful review of all records, which included a clinical history, physical examination, electrocardiogram and routine heart-chest x-ray, was made. In many patients, the diagnosis is supported by a heart catheterization (789 cases), an angiocardiogram (266 cases), an operative procedure (649 cases), or a post-mortem examination (295 cases). For these reasons, these data offer a serious effort to avoid any significant error.

According to these criteria, 4,144 records were studied and the general distribution of heart diseases is compiled in fig. 2.

CLASSIFICATION OF DISEASES
— 4,144 CASES —

DISEASE OF THE HEART	NO CASES	%
CONGENITAL DISEASE	607	14.6
RHEUMATIC	1598	38.6
HYPERTENSION	455	11.0
CORONARY	1341	32.4
OTHERS	143	3.4
TOTAL	4144	100%

Figure 2

These data, of course, do not reflect the exact incidence and distribution of heart diseases in the population in general. But they do indicate the needs of our population for a cardiac unit for diagnosis and treatment.

Congenital Malformations of the Heart (607 cases)

In this series of 607 patients, 342 are female (56.3%) and 265 are male (43.7%). The difference seems to have some statistical significance. Forty-four percent of these patients were under the age of 10, 29% between 10 and 19 and 11.9% between 20 and 29. Thus, 84.9% of all patients hospitalized for congenital heart disease were less than 30 years old (fig. 3).

This fact indicates that a very small percentage of patients afflicted with a congenital heart disease survive after the age of 30. It is therefore imperative to treat these patients in infancy and give them, as soon as possible, the advantages of curative surgery.

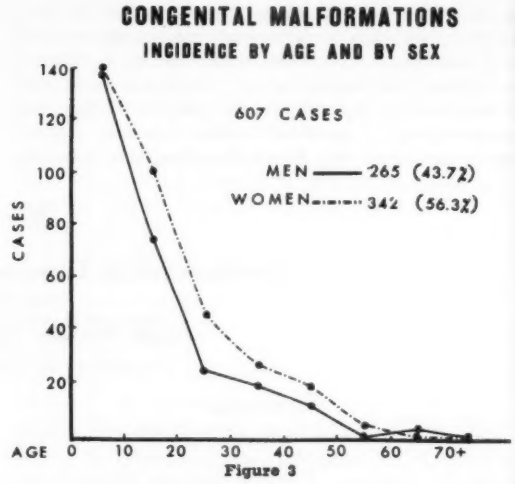


Figure 3

In order of frequency, the following malformations have been diagnosed:

1. Inter-auricular septal defect (I.A.S.D.) 151 cases — 24.9%
2. Inter-ventricular septal defect (I.V.S.D.) 102 cases — 16.8%
3. Fallot Diseases (Trilogy, Tetralogy and Pentalogy) 93 cases — 15.3%
4. Patent Ductus Arteriosus (P.D.A.) 74 cases — 12.2%
5. Coarctation of the Aorta (Co.A.) 32 cases — 5.3%
6. Others 155 cases — 25.5%

The incidence of these six types of congenital malformations were studied in regard to sex. The findings are tabulated in fig. 4. In this series, the female preponderance with respect to the incidence of inter-auricular septal defect (68.2%) and of patent ductus arteriosus (78.4%), and the highest incidence of coarctation of the aorta (68.7%) in the male are well illustrated.

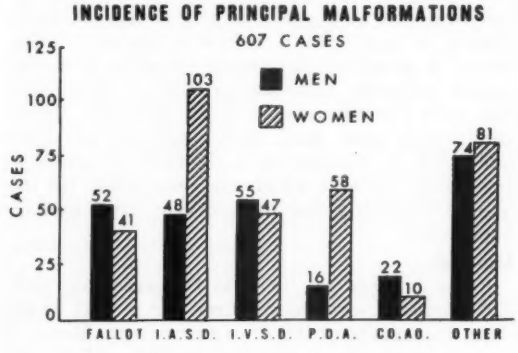


Figure 4

Looking back at the classification of congenital heart malformations, it can be seen that the first five groups of patients can now be operated upon successfully. This statement is especially true

since the introduction of the surgical techniques of heart-lung pump or extra-corporeal circulation. With the availability of this remarkable tool, it is especially rewarding to think that three congenital hearts out of four can now be successfully operated upon with a prospect of great improvement or cure in most cases.

More research is needed to correctly diagnose and successfully treat the remaining 25% of congenital cardiac patients. It seems appropriate to note the tremendous progress made in the congenital heart field since the classical monograph written by Maude Abbott in 1936. Surgeons deserve our most sincere admiration for their accomplishments which have astonished the world and changed the prognosis of this entire chapter of cardiology. At the Institute, 174 congenital cases were operated upon with 19% mortality. In the last year, open-heart surgery has permitted a broadening of the scope of surgery, and the first fifty patients done with a heart-lung machine gave promising and rewarding results with an overall mortality of 22%. Eight deaths occurred in the first 19 patients while only three in the last 31.

Rheumatic Valvular Diseases (1598 cases)

This group of patients was the largest one (38.6%). It is felt that such a preponderance of rheumatic patients is explained by the remarkable progress of surgery in the last ten years and by the reputation acquired by the Institute in the management of these surgical procedures. The majority of these patients were referred for investigation and operative possibility. Commissurotomy in tight mitral stenosis now constitutes the only logical treatment and a long term follow-up (9 years) shows very remarkable results. Surgery of aortic stenosis has not given such encouraging results. It must be realized that most patients with this condition are referred in the advanced or nearly terminal stage of the disease with alarming symptoms such as anginal pain, syncope or acute pulmonary oedema. On fluoroscopic examination, most of them have a calcific valve. Two factors may improve the results in the future: first, the opportunity to examine these patients in the early stage of the disease, and secondly, the use of a heart-lung machine with the possibility of removing as much as possible the calcareous deposits.

Pure mitral insufficiency and mitral disease can now be successfully operated with the aid of the extracorporeal circulation technique. Six patients were thus operated on in the last six months with encouraging early results.

The problem of aortic insufficiency has not yet been attacked at the Institute. Research is surely needed in order to find a surgical technique with a physiological approach. With the aid of extra-corporeal circulation, the day may come when the entire aortic valvular apparatus can be replaced.

In this series of 1598 patients, 41.5% were male and 58.5% female. The higher incidence in women

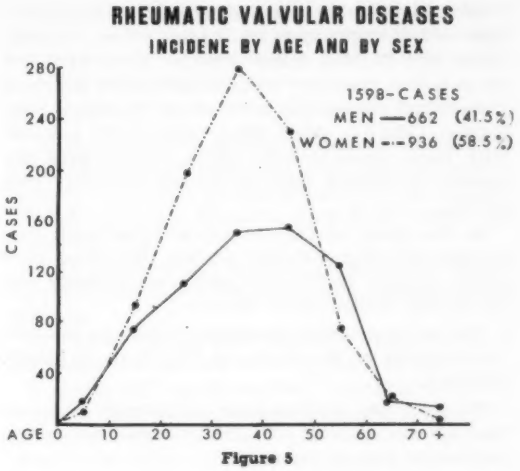


Figure 5

is statistically significant (fig. 5). Seventy-eight per cent of women and 76% of men who were hospitalized for their rheumatic valvular disease were under the age of 50. A detailed study of the age of these patients showed:

1.6%	1 day to 9 years
10.4%	10 years to 19 years
19.3%	20 years to 29 years
28.1%	30 years to 39 years
24.1%	40 years to 49 years
12.6%	50 years to 59 years
2.9%	60 years to 69 years
0.9%	70 years and more

The preponderant valvular lesion was the mitral in 73.5% and the aortic in 26.5% (fig. 6).

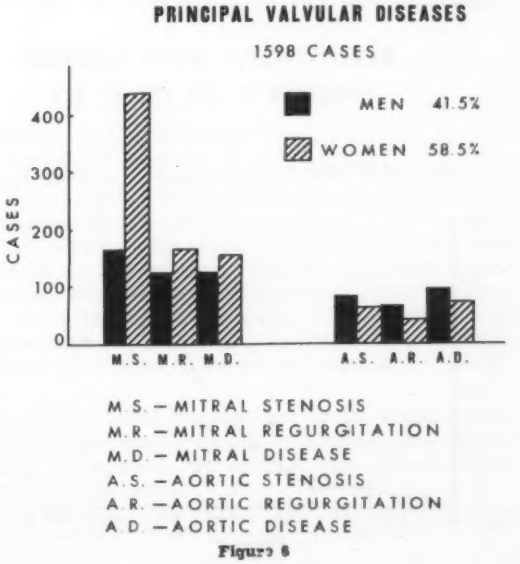


Figure 6

Of 1175 mitral patients examined, 51.5% had a pure mitral stenosis, 24.8% a pure mitral regurgitation and 23.7% a mitral disease. Over 64.6% of these mitral cases are women, and in the group of pure mitral stenosis the incidence of women is even higher, (72.5%). More than half of the patients with pure mitral stenosis (605) were offered the benefit of surgery with an overall mortality rate of 5%.

In the group of 423 patients afflicted with preponderant aortic valvular disease, 35% had pure aortic stenosis, 25.7% pure aortic insufficiency and 39.3% had mixed aortic disease.

Our series confirms the higher incidence of aortic involvement in the male (58.1%) than in female (41.9%).

We have not yet found any satisfactory explanation for the affinity of mitral disease for women and aortic disease for men.

Fifteen patients only were operated upon for their aortic stenosis with a mortality rate of 33%. These figures show our careful and ultra conservative attitude towards the surgery of aortic valve, and we hope that with the extracorporeal technique that a more encouraging future will be offered.

Hypertensive Heart Disease (455 cases)

This disease occupies the fourth place (11.5%) with respect to the incidence of cardiac patients hospitalized at the Institute. This incidence rate does not seem to represent the real incidence of this disease in the cardiac population at large. The present inquiry with the out-patients of the Institute may give a more realistic evidence of the importance of this disease. It is also interesting to point out that in our series there was a preponderance of men (55.2%) over women (44.8%). No explanation was found for this observation (fig. 7).

By decade the incidence of the disease for both sex was the following:

0.7%	1 day to 9 years
2.0%	10 years to 19 years
3.3%	20 years to 29 years
8.8%	30 years to 39 years
26.6%	40 years to 49 years
33.8%	50 years to 59 years
17.1%	60 years to 69 years
7.7%	70 years and more

Excluding coarctation of the aorta, which is considered in the section of congenital heart disease in this study, in only 4.5% was it possible to find the etiology of the high blood pressure.

Therefore, hypertension still offers a wide field for research. Nevertheless, remarkable drugs have been offered in the last ten years for its medical treatment and relief. It is important to treat this disease as soon as a clear-cut and certain diagnosis has been made in order to prevent the cardiac, renal, and cerebral complications.

Coronary Heart Disease (1341 cases)

Coronary patients represented 1/3 of our hospitalized patients. It is felt that this percentage will be even higher in the study of outdoor patients. It is known that coronary disease is responsible in the United States and Canada for ONE death out of FOUR. It is surely the single most deadly disease in North America.

Under this classification, the three main clinical varieties of coronary disease have been grouped: coronary thrombosis (acute coronary insufficiency), impending infarction syndrome (subacute coronary insufficiency) and angina pectoris (chronic coronary insufficiency).

Of the total of 1341 coronary patients, 1015 are men (76%) and 326 are women (24%). The highly preponderant incidence of this disease in men is well illustrated in this series (fig. 8).

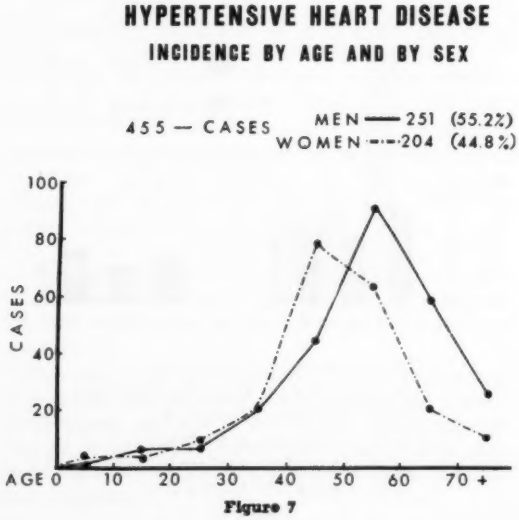


Figure 7

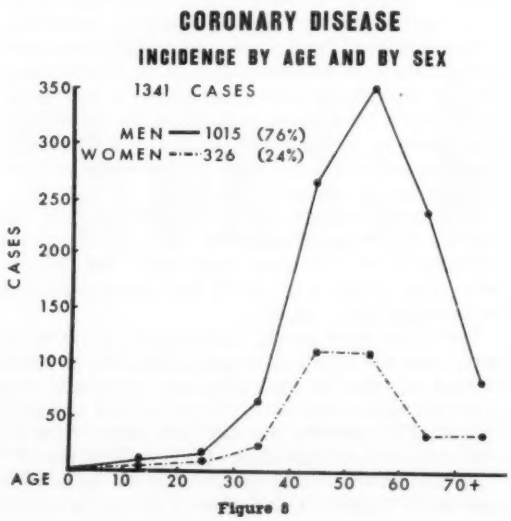


Figure 8

The incidence in the different decades of life gives the following:

0% from 0 to 9 years
0.3% from 10 to 19 years
1.0% from 20 to 29 years
6.6% from 30 to 39 years
28.3% from 40 to 49 years
34.6% from 50 to 59 years
20.8% from 60 to 69 years
8.4% from 70 and over

It may have some importance to point out that 36.2%, more than 1/3 of all these coronary patients, were less than 50 years old and more than 2/3 less than 60 years old, at the time of admission. This fact illustrates the fallacy of associating coronary disease with old age.

Coronary disease surely offers one of the more challenging problems of research in cardiology. Atherosclerosis is the cause of this disease which is responsible for too many premature deaths and disability. Unfortunately, the diagnosis of atherosclerosis is made only with the appearance of symptoms and too often at a late stage of the disease. On the other hand, two main contributions have helped in recent years: the use of anticoagulant drugs to prevent thrombotic extension and complications, and a better knowledge of the metabolism of fats which permits the lowering of blood cholesterol level in hypercholesterolemic patients. But, much more data, experimental and clinical, are needed to assess properly the value of these therapeutic measures, and a good deal more of research is needed to understand even the fundamental facts of atherosclerosis.

Other Heart Diseases (143 cases)

This group comprises diseases of the aorta (40 cases), pericarditis (55 cases) and cor pulmonale (48 cases). The incidence of these three entities was much higher in men (65.7%) than in women (34.3%). The number of cases remains too small for statistical purposes, but is high enough to be included in this study.

Summary

An analysis of all records of hospitalized patients in the Montreal Institute of Cardiology was undertaken to determine the incidence, sex, age and distribution of heart diseases. This study shows the following facts:

1. An almost equal number of men and women require hospital treatment for their cardiovascular diseases.

2. At the time of their hospitalization, 44.3% of the patients were less than 40 years of age.

3. Congenital malformations represent 14.6% of the total number of patients hospitalized and 85% of these were less than 30 years of age. The present surgical facilities can be advantageously offered to three out of four patients with congenital heart disease.

4. Rheumatic valvular lesions constitute the most important group of patients in this series. Seventy-eight per cent were less than 50 years old. Surgery was offered to 25% of these rheumatic patients.

5. Out of 455 patients hospitalized for hypertensive heart disease, 41.4% were less than 50 years of age.

6. The preponderance of male patients afflicted with coronary heart disease is clearly demonstrated by the fact that in a series of 1,341 cases, 76% were male.

7. A study is now being carried out in respect of outdoor patients. It is felt that the data of these two studies will contribute to give the picture of heart diseases in the Province of Quebec, especially in the French speaking population.

♥ ♥ ♥

On the French Contribution to Cardiology

"For my third and last subject, it is my pleasure to say a little more about the course of cardiology in France in recent years. Following Potain there has been an unfailing sequence of distinguished cardiologists among French physicians. First came pure clinicians like Merklen and Huchard, but it was the work of Vaquez, who combined the traditional French 'clinique' with the physiological methods and researches of Marey and François Franck, that marked the beginning of contemporary French cardiology. Apart from Laubry himself, to whose achievements I will return, we record with admiration the fine influence of Clerc, the brilliant observations of Gallavardin of Lyons, in clinical cardiology, and the example of Giraud. Then I would draw your attention to the constancy and the quality of the work of Professor Lian, a physician remarkable for his clinical discernment. These have been followed, in strength, by Soulié, Lenègre, Froment, Heim de Balsac, Routier, and others.

"The contributions of France would be more widely evident today if it were not for the unfamiliarity of the English-speaking countries with that graceful language. We should all gain by a hearty understanding with France, une entente cordiale médicale. The place of France in the civilized and cultural world cannot be shaken by the passing effects of war or by political vicissitudes."

—SIR JOHN PARKINSON: Leadership in Cardiology. The Charles Laubry Lecture delivered at the Second International Congress of Cardiology, Washington, D.C., on September 17, 1954. (Circulation, 11: 677, 1955.)

Arteriosclerosis and Ischemia
Pathological Considerations

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Among the diseases due to ischemia those attributable to arteriosclerosis are common. Research in these fields may be directed either towards the prevention, mitigation or cure of the effects of ischemia or towards the factors causing it. Arteriosclerosis of the intima appears to cause ischemia either by narrowing vessels of small calibre such as the smaller coronary arteries, renal or cerebral arteries, by narrowing arterioles, or by inducing thrombosis and occlusion in arteries of moderate calibre such as the larger coronary arteries, the popliteal, the carotid, vertebral or cerebral arteries. In general, the patterns of ischemic disease are different when the mechanisms of ischemia are different.

Many investigators do not distinguish between ischemic disease and hardening of the arteries—and, indeed, since intimal arteriosclerosis is difficult or usually impossible to diagnose except at autopsy, there may be some justification in attempting to assess a cause from an effect. To the pathologist, however, the association between ischemic disease and arteriosclerosis is not close enough to justify precise quantitative or qualitative conclusions although certain general conclusions may be warranted.

Indeed, arteriosclerosis of the intima is a process of such pleomorphism that it has not yet been classified satisfactorily. Many pathologists are of the opinion that it is not a distinct entity, that there is no constant pathogenesis and that there are at least three major etiologic patterns that, alone or in some combination, may influence the development of lesions. Because of the practical importance of arteriosclerosis, it is advisable to review from time to time the pathological anatomy of the lesions and to use it as a reference against which to assess the various hypotheses that may be proposed to explain some part of the disease. In the condensed descriptions and comments that follow the author has used the findings and opinions of many investigators in association with his own experience.

Small, focal fatty or fibrous lesions of the intima of the aorta or coronary arteries are found occasionally in infancy. These lesions become common in childhood and universal in young adult life. While it has been known for many years that the aortic intima commonly shows fatty flecks and streaks in childhood, it has only recently been found that fibrosis of the intima does not necessarily go hand in hand with such fatty lesions. Holman and his Associates[1, 2] have observed that in some populations fibrosis of the intima became prominent in young adult life whereas in others it does not, although both populations may have had about the same incidence of fatty lesions. The small fatty lesions in the upper aorta usually do not become prominent and may apparently regress whereas those in the lower aorta progress, and upon fibrosis become indistinguishable from lesions common in the adult. Such small lesions occur in adult life as well as in childhood.

The importance of the small fatty lesions lies in the fact that they represent an early stage of arteriosclerosis that may regress, may remain more or less static or may progress and induce a reactive fibrosis. They have given rise directly or indirectly to three important hypotheses about arteriosclerosis. The first hypothesis holds that the fat present in these lesions is derived from the plasma. This imbibition hypothesis maintains that a focal overload of the intima with lipid in the nutrient plasma results in its accumulation in the intima. Consequently, a hyperlipemic state, a dyscolloidal state of the plasma, or an injury to the arterial wall that interferes with the percolation of nutrient plasma through the intima may be expected to promote fatty arteriosclerotic lesions. Examples of each of these circumstances may be found in human and in experimental arteriosclerosis. The second hypothesis holds that the lipid in the small fatty lesions is a local product of metabolism by cells of the intima or media. There is evidence from biochemical studies that some species do have an appreciable production of phospholipids by the arterial wall and that lesser amounts of cholesterol and possibly triglycerides may also be produced. There is also evidence that the lipids in the lesions resemble but are not identical with those in the plasma and that the lipid composition of small and large lesions is not identical. It may be noted that the existence of a local metabolic production hypothesis does not exclude the imbibition hypothesis. Indeed, the two hypothetical mechanisms may act together. The third concept that emerges from the observations of the small fatty lesions in that some of them may regress leaving, it is thought only a trace of intimal fibrosis at their previous location. There is evidence both from human pathology and from experimental animals to support the idea that arteriosclerosis can be cured by regression of the lesions. Unfortunately, it would appear that more advanced lesions can be modified but that they will only undergo a limited regression.

For many years most investigators have thought that the fatty material accumulated in small arteriosclerotic lesions was irritating and that it caused a mild chronic inflammatory reaction and fibroblastic proliferation. This does, indeed, seem to be true, but it has been suggested recently that not all

of the lipids are equally irritating and that not all of the fibrosis on the surface of a lesion is necessarily a reaction to the underlying lipid. Particular emphasis has been placed in recent years by R. H. More and his associates[3] on the focal accumulation of proteinaceous materials in the intima of the aorta in areas free of lipid as well as in areas adjacent to lipid. It is the fate of such material to be converted to fibrous tissue and to yield hyaline fibrous lesions. Such lesions are common. The process is analogous to the organization of interstitial exudates in other tissues. Some lipid may be accumulated subsequently in such lesions. The importance of the recognition of this type of lesion lies in the fact that it provides an additional hypothesis for the development of lesions that are ab initio different from the fatty ones. The cause of the lesions is usually impossible to determine, but it may be some irritant other than lipid or some other cause of local intimal oedema.

The third method by which intimal arteriosclerotic lesions may arise is by the deposition on the intima of fibrin or thrombus material as a surface accretion or mural thrombus. Such encrustations subsequently may possibly be removed by proteolytic enzymes (i.e. plasmin) or they may be covered by endothelium and organized by fibrous tissue to form focal arteriosclerotic plaques. Lipid may subsequently accumulate in such lesions. There is no agreement among pathologists as to how often this mechanism may initiate lesions. In recent years Duguid and his followers[4,5] have advocated strongly the concept of the initiation of arteriosclerotic lesions by intimal surface thrombus formation. Nevertheless, the early lesion is, in my opinion, not frequently encountered in human arteries, it does not occur in experimental cholesterol atherosclerosis in rabbits and, although veins are particularly prone to thrombosis, they do not suffer from a phlebosclerosis analogous to arteriosclerosis. Many North American pathologists regard the process as one that is often secondary to some antecedent arteriosclerotic lesion in the aorta, frequently contributing to the enlargement of lesions but seldom initiating them. In any case, this different mechanism for initiating lesions is well recognized.

Other hypotheses to explain the initiation of lesions also exist as do hypotheses concerning the earliest of antecedent focal variations or changes in the intima. However, factual knowledge concerning them is too scanty to make their discussion useful.

Once the lesions of intimal arteriosclerosis are initiated, their progression may be very variable. There is evidence that progression may involve any of the pathogenetic mechanisms described above, that these may occur in any sequence or combination and that they may be episodic, intermittent or continuous. Furthermore, a variety of degenerative changes such as calcification or necrosis may occur in the lesions to render them yet more pleomorphic The lesions in a given patient reflect the etiologic mechanism that lies behind them only if this has been prominent. For example, an individual with marked hyperlipemia may show prominent fatty lesions while an individual with hypertension and low serum lipids may have chiefly fibrous and hyaline lesions. In general, however, the lesions observed in a patient at autopsy are pleomorphic and of varying etiology and represent the erratic development, arrest and progression of arteriosclerosis over many years of the patient's life.

It must be noted that the distribution of arteriosclerosis in the arterial bed is also very variable. While a well-developed etiologic agent such as marked hyperlipemia will affect much of the arterial tree, patients in whom no such etiologic agent can be identified often show striking differences in the incidence and severity of lesions in different parts of the arterial tree. The pathologist often sees quite different degrees of arteriosclerosis in the aorta, coronary and cerebral arteries in the same patient. Any of the three territories may be much the most severely involved. It is true, however, that there is a tendency for severe lesions in one territory to be accompanied by severe lesions in other arterial territories.

The pleomorphism of arteriosclerotic lesions, their variable pathogenesis, and their variable distribution makes the problem of quantitation most difficult. Unless a most exhaustive study is made at autopsy, it is quite impossible to provide any useful quantitative (or qualitative) estimate of the amount, types or distribution of arteriosclerosis found in a patient. Very few laboratories are prepared to undertake such studies. However, if attention is confined to some small part of the arterial tree such as the abdominal aorta or the coronary arteries, crude but useful estimates can be given. It is because of such restricted studies that the pathologist recognizes an association, somewhat variable, between arteriosclerosis and ischemic disease.

Ischemic disease of the heart, kidneys, brain or legs depends in part on the metabolic requirements of the organ or limb, in part on the adequacy of the general circulation, in part on the anatomy of the local vascular bed and its anastomotic connections, and in part on the luminal capacity of the arteries that normally supply the region. The latter consideration is frequently an overriding one. The association between ischemic disease and arteriosclerosis is such that it rarely occurs when arteriosclerosis is absent or is of slight degree in the local arterial bed, and it occurs with an increased frequency in the presence of moderate or advanced arteriosclerosis of the local arteries. Where one is considering vessels of small calibre (i.e. the kidney), the association is close, but where one considers vessels of larger calibre (i.e. the

major coronary arteries), the association is less close and thrombosis is a factor of major importance. In the case of the coronary arteries, ischemic disease is very rare in the absence of moderate or severe arteriosclerosis. Contrarily, many, indeed most, severe lesions may exist for long periods of time without inducing either ischemic heart disease or occlusive thrombosis. Nevertheless, when ischemic heart disease does eventually ensue it is almost always because of arteriosclerosis in the coronary arteries and usually in association with an occlusive thrombus.

Ischemic disease serves rather to locate arteriosclerosis than to quantitate it or to characterize it. It is useful to re-emphasize this fact. Arteriosclerosis can only be studied adequately at autopsy; something can be inferred about it from its association with ischemic disease, but the inferred conclusions may be erroneous. One may question whether some epidemiological and clinical studies of ischemic disease that purport to be investigations of arteriosclerosis have promoted or hindered our understanding of arteriosclerosis. This is not to denegate the studies as investigations of clinically important ischemic disease nor to deprecate their conclusions with reference to ischemic disease.

Indeed, many pathologists and other investigators feel that the conclusions to be derived from the study of ischemic diseases are urgently needed and are of great practical value. For example, when it is possible to prevent thrombosis in coronary arteries, ischemic heart disease may be postponed, perhaps until unusually advanced and stenotic arteriosclerosis has finally developed. Again, recent epidemiological studies[6] have indicated that a middle-aged man who is over-weight, hypertensive and hypercholesterolemic is a "high-risk" patient who has about one chance in two of developing coronary heart disease during the age period between 45 and 64. On the other hand, an individual without these abnormalities is a "low-risk" patient who has about one chance in twenty of suffering from clinical coronary heart disease during this period. It is not yet known, however, whether the frequency of coronary heart disease can be drastically reduced for the high-risk individual by the correction of one or more of the abnormalities mentioned above. Studies now in progress will take some time to yield clear answers to this question. Investigations of ischemic diseases in diabetes mellitus have indicated that peripheral gangrene is 50 times more common, that coronary heart disease is 3 to 4 times more common, but that cerebral vascular accidents are not any more common among diabetics than among non-diabetics. These striking changes in the frequency and in the distribution of occlusive disease in diabetics remain largely unexplained. While diabetic individuals have an increased amount of fatty arteriosclerosis, this increase seems inadequate to explain either the increased incidence of ischemic disease or the failure of cerebral ischemic disease to be increased in frequency. Ischemic renal disease has been a subject of active and useful research for many years.

The practical reasons for attempting to state precisely the pathological distinctions between intimal arteriosclerosis and ischemic disease arising because of local complicated arteriosclerotic lesions are several. The distinction serves to emphasize that intimal arteriosclerosis is common, complex, polyetiologic and variable in its pathogenesis. It serves to emphasize that the disease of clinical interest is the ischemic disease and not the underlying arteriosclerotic lesion. The distinction also serves to emphasize that while moderate or severe arteriosclerosis is generally a sine qua non for the occurrence of ischemic disease, it will not usually cause ischemic disease (except when in the smallest vessels) unless it is further complicated by thrombosis, ulceration or intramural haemorrhage.

Theoretically, from the point of view of prophylaxis, the distinction indicates that one may seek to prevent the initiation of arteriosclerotic lesions by any of the three initiating mechanisms referred to above; one may seek to prevent their progression once initiated; one may seek to prevent the occlusion of arteries by complications such as thrombosis or intramural haemorrhages; or one may seek to prevent or mitigate the effects of ischemia on an organ or tissue. Some of these theoretical considerations have already found some practical application in modern medicine.

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Dietary Factors in the Regulation of Serum Cholesterol Levels in Man

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It is now well established that serum cholesterol levels vary widely in different parts of the world, and are more closely related to the dietary fat intake of the populations studied than to any other of their distinguishing characteristics[1]. The quality of the fat consumed and particularly its degree of unsaturation seem to be the most important factors in accounting for the cholesterol levels observed.

Corn oil is the most potent of the cholesterol depressants studied to date; its effect cannot be accounted for entirely on the basis of the content of unsaturated fatty acids. Other factors are undoubtedly involved[2]. Is this a specific effect of the "essential" fatty acids, linoleic, linolenic and arachidonic, or a non-specific effect related only to the degree of unsaturation of the constituent fatty acids? Ahrens et al[3] found just as great an effect on serum lipids whether corn oil (rich in EFA) or menhaden oil (almost devoid of EFA) was fed. Indeed the only chemical structure which is common to menhaden, corn, whale, sardine, pilchard, cotton seed, linseed, soyabean, peanut, safflower and sunflower oils (all of which cause depressions of serum cholesterol levels in man) is POLY-UNSATURATION. The only conclusion that can be reached at present is that this is a non-specific effect of all cis methylene — interrupted double bonds.

The mode of action of the unsaturated oils in lowering serum cholesterol appears to be related in part to the intestinal recycling of sterols. Corn oil has been shown to result in an increased excretion of labelled cholesterol[4] or bile acids[5] in the faeces in amounts roughly proportional to the fall in serum levels.

It is not clear at present whether the hypocholesterolemic effect of certain unsaturated fats is a positive effect or a neutral one, i.e. resulting solely from the removal of saturated fats and associated substances and their replacement by the unsaturated variety. Possibly, a combination of factors is involved.

Materials and Methods

Our subjects with few exceptions were student volunteers in good health, who carried on with their regular duties during the experiments. During the control periods the subjects recorded their dietary intake on diet history forms after instruction by the dietitian. Total calories, as well as the percentage of calories taken as fat, protein and carbohydrate were then calculated from standard tables. During the study periods of one to three weeks a basal low fat diet was used to which the fats, fatty acid esters or other test substances were added. (See Table 1). All diets were isocaloric for each individual and the protein content was held constant. Subjects were weighed twice a week and caloric intake adjusted to keep the body weight constant during the experiments. In one series of experiments formula diets were used; the basic formula was similar to that described by Beveridge et al[6]. Lipids were estimated twice a week on serum obtained in the fasting state. In some instances, faeces were pooled daily for faecal fat estimation. Serum cholesterol was determined by the method of Abell[7], serum triglycerides by Van Handel and Zilversmit's method[9] and faecal fat by Van der Kamer's method[10]. Lipoproteins were determined by paper electrophoresis[8].

Table 1
The Average Distribution of Calories in, and Cholesterol Content of, the Control and Low-Fat Diets

Diet	Percentage of calories yielded: Protein	Fat	Carbohydrate	Cholesterol (mg.)
Control	14	45 a	41	512
Low-fat	16	4 a	80	28

a By analysis; all other figures from tables.

Results

1. The effect of adding corn oil to a low fat diet (Fig. 1)

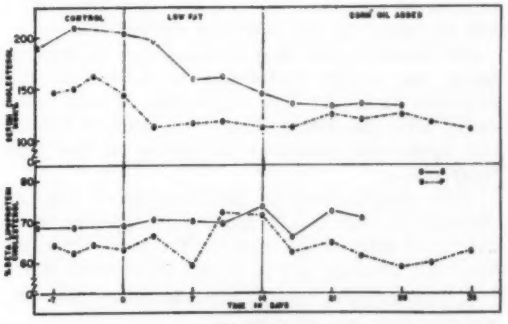

Figure 1
The effect of corn oil supplements after two weeks on a low fat diet. Details and discussion in text.

Two male subjects, S and P, received the low-fat diet for a two-week period. Subject P then received 10 gm. increments of corn oil every three days up to a total of 70 gm. (23.7% of calories) at the end of the experiment. Subject S received 40% of his calories as corn oil from the start of the test period. Whereas both subjects showed a drop in serum cholesterol during the low-fat period, there was no further change during the corn oil administration. Similar short term studies with six

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additional subjects failed to show any appreciable change from the levels of cholesterol achieved on the low fat regime. (See Table 2).

Table 2
Mean Values of Serum Cholesterol for Consecutive Dietary Periods

	Control Period	Low Fat Period	Corn Oil Period
Duration of period	1 week	1 week	2 weeks
No. of subjects	6	6	6
No. of determinations	2	2	4
Serum Cholesterol mgm%	204.5*	157.5*	155.7*

*Mean value for each period.

In summary, our experiments suggested that corn oil played a neutral or passive role, and that the drop in serum cholesterol observed was essentially due to the removal of saturated fats or associated substances from the diet.

Table 3
Changes in Beta lipoprotein Per Cent with Consecutive Dietary Periods

	A		B		C	
	Control	Corn Oil	Control	Low-fat	Low-fat	Corn Oil
Subjects	8	8	14	14	6	6
Observations	23	25	53	56	19	20
Mean	72.6	66.8	75.45	75.80	71.06	67.25
S.D. =	6.4	7.4	7.4	7.1	4.1	5.5
P.		0.1				0.2

In Table 3, we have summarized our data on lipoprotein distribution during different phases of the dietary experiments. (a) During the control period 72.6% of the total lipoprotein was present as B lipoprotein. The addition of corn oil to the diet reduced this figure to 66.8%. (b) In a second series of experiments with 14 subjects, B lipoprotein during the control phase was 75.4%. Institution of a very low fat diet did not change the percentage of total lipoprotein present as B lipoprotein although it substantially reduced total cholesterol. (c) Finally, in six subjects transition from low fat to corn oil diet resulted in a fall in B lipoprotein, but no apparent fall in serum cholesterol.

Our data suggests that whereas corn oil does not lower the serum cholesterol levels below those achieved on a very low fat regime, it does appreciably alter the distribution of cholesterol between the lipoprotein fractions, in favour of the alpha lipoprotein.

This stabilization of the cholesterol transport mechanism that results from the ingestion of unsaturated fatty acids may be far more important than the absolute fall in serum cholesterol itself.

2. The effect of adding ethyl linoleate and ethyl stearate to a low fat diet.

In an attempt to elucidate this problem, we next studied the effects of relatively pure esters of linoleic and stearic acids (Prototypes of an "unsaturated" and "saturated" fatty acid) on the serum cholesterol levels.

Ethyl linoleate concentrate (95% linoleate), ethyl stearate (hydrogenated linoleate concentrate), corn oil and butter fat were separately fed to each of four subjects at the end of two weeks on the low-fat regime (Fig. 2). The fats and oils were added to the diet in increments of 10 gm. every three days, except butter fat, which was given in increments of 20 gm. By the end of the experimental period, the subject on butter fat was receiving 80 gm. of added fat daily, while the other three subjects were receiving 70 gm. The proportion of total calories yielded was 26.4% for butter fat, 23.7% for corn oil, 25.2% for linoleate, and 25.7% for stearate. The added fat was given for twelve days (for the subject on butter fat) and twenty-one days (for the other three). Stools were collected throughout the experiment and analyzed for total fatty acid content.

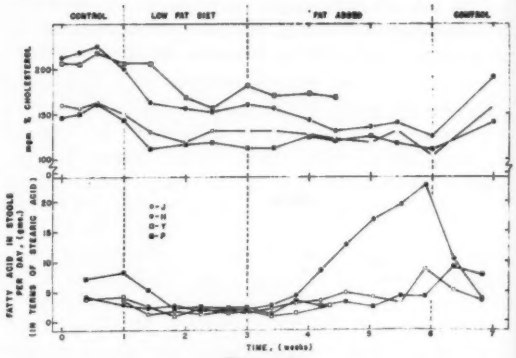

Figure 2

Effect of ethyl linoleate concentrate, ethyl stearate, corn oil, and butter fat on serum cholesterol and stool fat. J received ethyl linoleate, H ethyl stearate, P corn oil, and Y butter fat.

From the low levels attained on the low-fat diet, there was no discernible rise in the blood cholesterol with corn oil, ethyl linoleate, or ethyl stearate: in fact, with ethyl stearate there appeared to be a slight fall. Nearly all the butter fat and corn oil were absorbed (Fig. 2) and 65-70% of the stearate. Linoleate was well absorbed up to a dose of 60 gm. daily; when the dose was increased to 70 gm., there was a decrease in absorption. With butter fat, there was no significant change in the serum-cholesterol, and after ten days the levels were still well below control values.

Three more subjects were tested with ethyl linoleate in amounts yielding 40% of calories without any further fall in serum cholesterol from the levels achieved on the low fat regime (Fig. 3).

The fully hydrogenated product of ethyl linoleate, ethyl stearate, resulted in steatorrhoea and a further slight fall in serum cholesterol.

These experiments demonstrated that even very large amounts of ethyl linoleate had no intrinsic cholesterol depressant effect when applied on a low fat diet base. The result is in line with our previous conclusion that corn oil (and other vegetable oils) exercise only a "neutral" effect on serum cholesterol levels. It should be noted here that Kinsell[11] has carried out similar experiments which suggest an active depressant role for linoleate, so that the matter is not yet entirely resolved. The role of fully saturated fatty acids proved more difficult to determine because of their poor absorption from the gastro-intestinal tract.

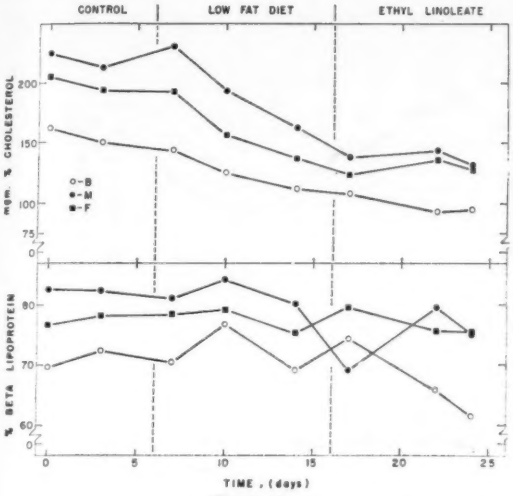

Figure 3

Effect of ethyl linoleate concentrate on the serum cholesterol following a preliminary period on the low fat diet.

3. The effect of natural modification, and processing of foodstuffs on the serum cholesterol levels

Despite the fact that the mechanism of its action remains obscure, there is no doubt that the substitution of corn oil for the saturated fats of the diet results in a fall of serum cholesterol levels of 20-30%. It would seem desirable therefore to carry out such a substitution in our daily diet. Human dietary patterns however, are notoriously difficult to change. The mere addition of large amounts of corn oil to the regular diet has variable effects on the serum cholesterol and may result in obesity. Low fat diets tend to be uninteresting, unpalatable and socially unacceptable. It occurred to us, that this problem could be attacked by altering the composition of the fat of commonly used foods, either by natural means i.e. incorporating unsaturated fatty acids into the diet of hens, cows, pigs, etc. or by processing foods prior to marketing.

In collaboration with J. B. O'Neil of the Poultry Science Division, we fed 10% sunflower seed oil to hens for an eight-week period. Eggs collected after ten days on this diet were examined by the gas chromatographic method and showed a six-fold increase in the di-unsaturated C^{18} fatty acids which was almost entirely due to linoleic acid (See Table 4).

Table 4
Fatty Acids of Yolk Fats

Name of acid	No. of carbon atoms	No. of double bonds	Control %	Experimental %
Probably branched	6	0	7.45	6.00
Caproic	6	0	0	0
Myristic	14	0	0.33	0.36
Palmitoleic	16	1	3.08	1.36
n-Hexadecanoic	16	0	26.7	21.80
Linoleic and linolenic	18	2 & 3	5.65	30.40
Oleic	18	1	46.9	28.00
Stearic	18	0	8.64	9.90
Arachidonic	20	4	1.28	2.54

These eggs were next subjected to dietary trials using both natural base and formula type diets. Although there was some suggestion of a lesser cholesterogenic effect from the special eggs, this was not enough to be significant. Data from the formula type diet experiment is shown in Fig. 4. In these experiments 40% of the calories were derived from yolk fats. Failure of the substantial increase in linoleic acid content to lower the serum cholesterol levels is probably due to the high content of cholesterol and phosphatidylethanolamine in the egg yolks. Attempts to lower the cholesterol content of the yolks by feeding hens large amounts of nicotinic acid (up to 1.2 gms./day) have not been successful.

Additional studies have been carried out by processing milk products to remove the butter fat and replace it with corn oil. With the co-operation of Dr. Gibson of the Dairy Science Department, corn oil ice cream and corn oil milk were prepared. When these products were fed to volunteers who had been on a low fat basal diet for one week, there was no rise in the serum cholesterol levels from the low values achieved on the low fat diet. Feeding natural milk and ice cream in similar amounts (40% of calories) resulted in a rapid return of cholesterol to control levels. (Table 5).

Table 5
Dietary Tests with Commercially Processed Food Products
Serum cholesterol levels obtained with groups of healthy volunteers (4 subjects/group)

Series	Product	Control Period one week	Low fat Period one week	Test Period two weeks
A	Corn oil milk and ice cream	213*	161**	157***
	Natural milk and ice cream	219	177	222
B	Corn oil margarine	214	172	221
	Butterfat	194	155	196
C	Corn oil margarine	210	156	186
	Commercial margarine	205	161	183

*Average of at least three determinations per subject.
**Final determination at end of low fat period.
***Final determination at end of test period.

Studies are now under way on a new partially hydrogenated corn oil margarine*. This product has an iodine number of 95.0 as compared with a standard commercial margarine with an iodine number of 88.4 (natural corn oil iodine number 122-125 and butter 30-40). The results from three separate sets of dietary experiments are shown in Table 5. Separate groups of four subjects were studied on each occasion. Test B in which corn oil margarine was tested against butter showed a rapid return of cholesterol levels to control values at the end of the two-week test period in both groups. Test C in which corn oil margarine was compared with commercial margarine showed only partial return of serum cholesterol toward control values. In contrast, are the results in test A in which pure corn oil was used, with no rise at all in the cholesterol levels from the low point achieved on the low fat diet. It would appear that even partial hydrogenation of corn oil may seriously affect its properties and render it cholesterogenic.

*(Best Foods 'Cornette').

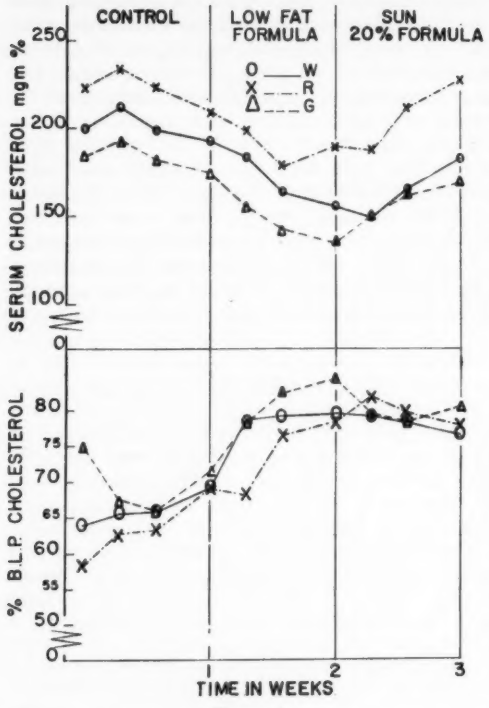

Figure 4a

Formula diet providing 40% of calories from egg yolk fat. Eggs obtained from hens fed 20% Sunflower seed oil in their diet.

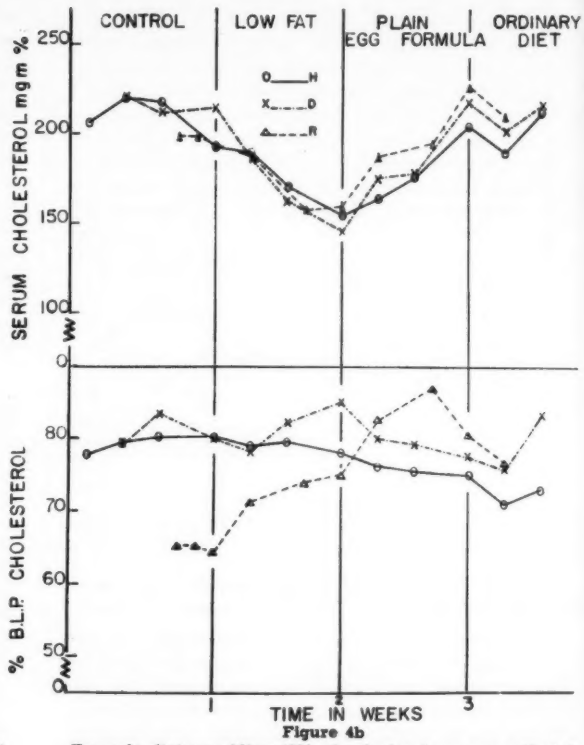

Figure 4b

Formula diet providing 40% of calories from egg yolk fat. Control eggs from hens fed commercial laying ration.

The chemical changes produced by hydrogenation are not fully known, but include the following: (a) hydrogen is added at double bonds, lowering the iodine number, (b) the double bond may shift its position along the carbon chain producing iso-acid forms, (c) the predominantly occurring CIS configuration may change to the trans-configuration, (d) with linoleic, linolenic or arachidonic acids there may be conjugation, in which system the double bonds are not separated by a methylene group. Our dietary studies suggest that the "isomers" produced by hydrogenation have a different effect on cholesterol metabolism than do the naturally occurring fats in untreated corn oil. It is entirely conceivable that apart from the isomer's being non-equivalent and therefore a non-substitute, it may act as a metabolic antagonist to the natural form.

Recently Brown and Page[12] reported studies on an experimental nonhydrogenated vegetable oil product which could be used as a spread, and also as a satisfactory substitute for butter in cooking and baking. The use of vegetable oil filled milk or ice cream, and the substitution of nonhydrogenated semisolid vegetable fat in spreads or for cooking should make it possible to produce a palatable diet low in animal fat and rich in unsaturated fatty acids. Brown and Page[12] have reported their experience with such diets which have a high degree of patient acceptance and result in satisfactory and sustained depression of serum cholesterol levels.

Summary and Conclusions

It now appears possible to design attractive diets containing our customary fat complement (about 40% of calories) which will permit a fall of 20-30% in ambient serum cholesterol levels. This may be achieved mainly by processing of dairy fats and by preparing non-hydrogenated semisolid and solid vegetable fats for spreads, cooking and baking. Our own studies lead us to believe that the fall in serum cholesterol which results is entirely due to removal of saturated fats and cholesterol from the diet, permitting the serum cholesterol to fall to its "natural baseline". Whether such diets will prevent the progression of atherosclerosis remains to be seen. Certainly there is some evidence that unsaturated fats may favourably affect the clotting mechanism in man[13]. Long term clinical trials using such diets are entirely justified and are now under way.

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Lipids, Blood Coagulation and Atherosclerosis

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Of the many experimental approaches to the problem of atherosclerosis, one which is of some interest is the encrustation theory of Rokitansky[1]. Although this concept was not given much emphasis following its inception, the recent work of Clark, Graef and Chasis[2], Duguid[3,4,5], Crawford and Levene[6], Morgan[7], and Haust, More and Movat[8], has provided evidence that fibrin deposits do play a role in the development of atherosclerotic plaques. The work of Haust and associates[8] demonstrated that some of the early lesions consist mainly of fibrin and platelets. Therefore, it does not seem unreasonable to suggest that one way an atherosclerotic plaque may develop is by the incorporation of small deposits of platelets and fibrin into the intima.

There is evidence that the formation of platelet and fibrin thrombi is determined in part by the nature of the coagulation mechanism and vessel surfaces[9]. The possibility that lipids may influence this process is suggested by the fact they play a role in blood coagulation[10]. (Normally this is provided by the platelet). Recently, it has been shown that phospholipids are important in this problem. Phosphatidyl ethanolamine (P.E.) has been found by several investigators to promote clotting[11,12,13,14], while phosphatidyl serine (P.S.) has been found to have either no effect or an anticoagulant effect[13, 14, 15]. However, others have reported that P.S. has a clot promoting effect and P.E. little or no activity[16, 17]. These apparently discrepant findings seem to be in part due to differences in methods of preparation, analysis and testing. Until such time as pure compounds of known structure become available, this problem will not be completely resolved. Our own studies have shown that P.E. has definite clot promoting characteristics while P.S. over the same concentration range has a definite anticoagulant effect both in vitro and in vivo. Furthermore, our studies have shown that phospholipids influence primarily the first stage of clotting which involves the platelet.

The mechanism of coagulation can be divided in several ways but to understand the relationship between clotting changes and the formation of platelet and platelet-fibrin thrombi the mechanism is best divided into two stages. The first stage consists of the changes prior to the onset of platelet clumping (platelet viscous metamorphosis), the initial stage in the formation of platelet thrombi and the second stage consists of the subsequent changes prior to the onset of fibrin formation. During the first stage when blood clots in a tube one of the earliest changes[18] is an increase in Factor IX (Christmas factor, P.T.C.) activity which is associated with an increase in platelet adhesiveness. (Presumably Hageman Factor increases in activity during this phase but we have as yet been unable to disassociate these changes from those of Factor IX). After a period of four to five minutes, the platelets clump and viscous metamorphosis occurs. Following platelet clumping, there is a marked decrease in platelet adhesiveness. About 40 seconds following the onset of platelet clumping, Factor VIII (AHG) and Factor V (accelerator-globulin, labile factor) activities disappear, while Factor VII (stable factor) activity increases. Detectable thrombin formation occurs at this time and is followed shortly thereafter by fibrin formation. No detectable changes occur in the prothrombin and Russell viper venom times until after fibrin formation occurs. This evidence demonstrates that during the rather long period prior to the onset of platelet clumping two of the main changes are an increase in Factor IX activity and platelet adhesiveness. It seems reasonable to interpret changes in either of these indices as evidence of the nature of clotting activity in this stage. Furthermore, under the conditions of this type of study, it can be stated as a

fundamental law that the platelets have to clump before fibrin can be formed.

The early work of Bizzozzero[19] demonstrated that the material most readily deposited from circulating blood on damaged surfaces is the blood platelet. Subsequent studies[20, 21, 22] including our own have demonstrated that platelets are the material most readily deposited from circulating blood onto surfaces and that these deposits tend to occur at points where there are changes in blood flow. Furthermore, fibrin deposits from circulating blood do not normally occur until there has been platelet deposition[20, 22]. Therefore, the law which was true for blood coagulation in a tube seems to be also true for circulating blood, that is, platelet clumps or thrombi have to form before there are fibrin deposits.

In view of this, it would seem reasonable to look at the blood platelet as a factor in the early lesions of the encrustation type of atherosclerosis. Furthermore, the effect of lipids on the first stage of coagulation could influence platelet deposition. Increased activity of the first stage of clotting secondary to certain dietary fats could lead to increased platelet adhesiveness, and thus more numerous and larger platelet deposits. Therefore. if encrustations are a factor in the development of atherosclerosis, this should also be associated with increased atherosclerosis.

In the remaining part of the paper the following problems will be briefly discussed: one, lipids and coagulation; two, nature of coagulation in humans; three, animal experiments; four, phospholipids and blood lipid levels; five, platelet deposits and atherosclerosis.

Lipids and Coagulation

The in vitro effect of lipids on coagulation can be studied, using the thromboplastin generation. The lipid to be tested is used in place of platelets in the test system. Studies using the thromboplastin generation test have shown that while butter contains a lipid active in clotting, such fats as margarine, corn oil and cod liver oil do not. The activity of these fats in the test system appear to be related to their phospholipid content and the nature of the phospholipids[23].

In vivo studies[24] have shown that following the intravenous administration to swine of material rich in phosphatidyl ethanolamine, there is an increase in Factor IX activity, a decrease in Factor VIII activity and in the platelet count. However, following the intravenous administration of material rich in phosphatidyl serine, there is no apparent change in Factor VIII activity or the circulating platelet count, but there is a decrease in Factor IX activity. These studies show that phospholipids are one factor governing the activity of the first stage of clotting prior to the onset of platelet clumping.

Studies in man of the effect of feeding different fat preparations enriched with various phospholipids showed that Factor IX activity is increased following the ingestion of foods such as butter which are relatively rich in coagulant active phospholipid such as phosphatidyl ethanolamine[23]. However, following the ingestion of butter enriched with sufficient additional phosphatidyl serine to inhibit the P.E., there was a decrease in Factor IX activity. Therefore, it appears that phospholipid ingestion influences the activity of the first stage of clotting as manifested by changes in Factor IX activity.

Nature of Coagulation in Humans

In the fasting state, subjects with clinical complications of atherosclerosis or subjects with no clinical complications but a positive family history were found to have greater Factor IX activity than a matched control group with a negative family and clinical history for atherosclerotic vessel disease complications[25].

During the period of alimentary lipemia following a meal of dairy fats and eggs (rich in phosphatidyl ethanolamine), the groups with either a positive clinical or family history for atherosclerotic vessel disease complications showed a greater increase in Factor IX activity than the control group with the negative clinical and family history[26].

This evidence, in view of the changes which occur in the first stage of clotting, suggests that atherosclerotic subjects should have more adhesive platelets than a control group and that the nature of the diet influences platelet adhesiveness. McDonald and Edgill have reported findings which support this conclusion[27, 28]. Therefore, there appears to be some relationship between the activity of the first stage of clotting, platelet adhesiveness and atherosclerotic vessel disease complications in man.

Animal Experiments

Studies in monkeys[29, 30] and swine[31, 32] have shown that egg yolk rich diets cause a greater increase in lipids and more atherosclerosis than do diets rich in butter. The effect of butter on blood lipids is variable; in swine there is little or no change in blood lipids, while in the monkey, there is an increase. Margarine rich diets have little if any effect in either species in terms of blood lipid and clotting changes or increase in amount of atherosclerosis. Butter rich diets increase the amount of atherosclerosis in both animals, and, if monkeys are left on butter rich diets long enough, they develop thrombotic vascular occlusions[33].

Margarine contains very little phospholipid, butter contains coagulant active phospholipid, while egg yolk is very rich in this material. Therefore, the foodstuff with the greatest coagulant active phospholipid content has the greatest effect on atherogenesis, while the fat with the least content has the least effect.

Although this evidence is in keeping with the hypothesis that increased platelet deposition because of accelerated clotting associated with the

ingestion of coagulant active phospholipid increases atherogenesis, it could equally well be explained on the basis of the cholesterol content of these foods. Egg yolk contains much more cholesterol than butter while margarine contains none.

The results of the study[32], comparing the effects on the development of atherosclerosis in swine of isocaloric diets of egg yolk or butter, were examined for evidence bearing on the lipid imbibition and encrustation theories of the pathogenesis of atherosclerosis.

On the lipid imbibition theory a positive relationship could be expected between the blood cholesterol level and percentage of aorta involved with atherosclerosis. Examination of this point showed such a relationship in the egg fed pigs. That is, the greater the increase in blood cholesterol the greater the amount of aorta involved. In the control animals, there was no such relationship (swine like man develop atherosclerosis regardless of the fat composition of their diet). In the butter fed group, the relationship was opposite to that of the egg fed group. That is, the less the change in blood cholesterol the greater the amount of aorta involved with atherosclerosis. Although this in no way disproves the imbibition concept, it does suggest that elevation of the blood cholesterol level is not a prerequisite for increased atherosclerosis and that it may be important as a secondary rather than primary factor.

On the encrustation theory, one could expect some relationship between change in Factor IX or platelet adhesiveness and degree of aorta involved. The feeding of eggs or butter to swine is associated with increased Factor IX activity. Examination of the relationship between degree of aorta involved and change in Factor IX activity showed a positive relationship in all three groups, but it was only significant in the egg and butter fed animals. Therefore, it would appear there may be some relationship in swine between the degree of aorta involved and the degree of change in the first stages of clotting which involves the platelet.

Another factor of considerable importance is the obviously marked effect egg yolk has on the development of atherosclerosis and changes in blood lipids and clotting in experimental animals[30, 32, 34]. It may be just the cholesterol content of eggs which is the factor, but there is evidence that there may be other factors. It is perhaps surprising that following the early rabbit experiments[35, 36] which demonstrated that cholesterol is a factor in atherogenesis in rabbits, no one has studied the effect of egg yolk in experimental atherosclerosis following removal of the cholesterol. Since we now have evidence the egg yolk is rich in phosphatidyl ethanolamine which could through the clotting mechanism also influence the course of atherosclerosis, it is obviously important that the factor or factors in egg yolk be clearly defined.

Phospholipids and Blood Lipid Levels

Amatuzio and Hale[37] reported that phospholipids, in particular those prepared from egg yolk, had an effect on blood lipid levels. They found that when egg yolk phospholipid was fed to susceptible subjects who were on low fat diets, there was a marked rise in the blood lipids. We have not found the feeding of material rich in phosphatidyl ethanolamine to raise the blood lipid level, but we have found that material rich in phosphatidyl serine lowers the blood cholesterol level[24]. These preliminary findings suggest that in addition to their effect on the coagulation mechanism, phospholipids may have some influence on the blood lipid level.

Platelet Deposits and Atherosclerosis

Some pathologists consider the early atherosclerotic lesion to be a swelling and increase in intimal metachromatic ground substance in which fine droplets of sudanophile lipid are present[38, 39]. The platelet contains metachromatic ground substance[40, 41] and lipid[42, 43] including cholesterol. Furthermore, as was mentioned in the first part of this paper, platelet deposits tend to occur at points where there are changes in blood flow such as bifurcations and vessel orifices. Therefore, a platelet deposit could resemble an early atherosclerotic lesion, both in terms of composition and location.

Another point of interest is the possible relationship of platelet deposits to fatty streaks. Studies using special silicone-coated plastic flow chambers have provided some data on this point[22]. It has been found that a platelet thrombus formed from circulating blood on the surface of a flow chamber will take a fat stain and resembles a fat streak. This evidence suggests that platelet deposits could give rise to fatty streaks on vessel surfaces. Furthermore, since platelets trap plasma during viscous metamorphosis, the amount of fat found in the deposit would in theory be greater in hypercholesterolemic than in normocholesterolemic states. It is possible, therefore, that the incorporation into the intima of platelet deposits could resemble an atherosclerotic plaque. Further deposits and change could lead to vascularization and intimal haemorrhage, more lipid accumulation, fibrin deposits, fibrosis and calcification.

Although the evidence and theoretical concepts which have been discussed suggest that there may be some relationship between dietary phospholipid (e.g., that contained in such foods as dairy fats and egg yolk) platelets and atherosclerosis, the evidence to date is too scanty to make a firm conclusion. However, it does seem important that the relationship be further explored and the exact significance with regard to the problem of atherosclerosis be determined.

Summary

Part of the possible relationship between dietary fat, blood coagulation and the encrustation theory of atherosclerosis has been discussed. Evidence has

been presented which indicates that, if encrustations are a factor in the development of atheroma, the platelet is an important initial factor. Platelet deposits resemble in many ways features of atherosclerosis including fatty streaks. Some dietary fats such as dairy fats and eggs influence the first stages of clotting, possibly because of their phospholipid content. Because these changes are associated with increased platelet adhesiveness they may lead to more numerous and larger platelet encrustations. However, the exact relationship between lipids, blood coagulation and the development of atherosclerosis remains to be determined.

Acknowledgment

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Diagnosis and Treatment of Impending Myocardial Infarction

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Prevalent among the serious problems contronting the practicing physician are those arising from ischemic heart disease. This disease results from occlusive coronary atherosclerosis, with or without thrombosis, and is characterized clinically by the syndromes of angina pectoris, coronary insufficiency and myocardial infarction. The most lamentable consequences are sudden death and myocardial infarction. Even with the use of all available measures, including anticoagulants, the mortality following acute myocardial infarction remains distressingly high. Until such time as the underlying cause of atherosclerosis can be prevented or controlled, the best hope at present for reducing mortality lies in the recognition of those patients in whom myocardial infarction is likely to occur and the initiation of any measures which may prevent such a development. This approach leads to an additional coronary syndrome, that of "impending myocardial infarction."

It has long been known that attacks of myocardial infarction are frequently preceded by premonitory pain. Soon after the introduction of oral anticoagulants in the treatment of acute myocardial infarction, several authors[1, 2, 3] conjectured that they might well serve an important role in the prevention of such attacks. Stimulated by the results of Wood[1] the present study was begun early in 1949; some preliminary observations were described in this journal in 1951[4]. Since then the authors have made the diagnosis of impending infarction in over 200 patients. As yet a detailed analysis[5, 6] of the first 100 patients only has been completed and discussion will be limited to these.

As the study progressed a number of problems emerged with clarity: the need for precise criteria for the recognition of impending infarction, the necessity for promptness in the attainment of anticoagulant control, and the desirability of a fuller understanding of the mechanism by which oral anticoagulants exert their effect. Additionally there was the major problem of determining whether or not the administration of anticoagulants in any way modified the outcome. Data relevant to these problems will be presented.

Diagnosis

Beginning with the earliest clinical studies on myocardial infarction it has been recognized that, although an attack often occurs without warning, there are frequent instances in which premonitory pain foreshadows the event. Obrastzow and Straschesko[7] in 1910 reported the case of a 57-year-old man who sustained myocardial infarction, proved by autopsy, which was clinically evidenced by brief attacks of anginal pain at rest, none of which lasted more than ten minutes. In 1912, Herrick[8] stated that ischemic myocardial necrosis of slight extent was often clinically manifested by mild anginal pain at rest. Following these early reports the published references to prodromal pain preceding myocardial infarction have been numerous. The literature on premonitory or preliminary pain in myocardial infarction has been recently summarized by Mounsey[9].

Mounsey[9] reviewed 139 cases of myocardial infarction and found prodromal pain in 40, an incidence of 29 per cent. This is lower than that of Sampson and Eliaser[10] and of Feil[11], in whose series it was 48 per cent and 50 per cent respectively, and higher than that of Yater[12] who found an incidence of 9.5 per cent in men under the age of 40. Mounsey suggested that this frequency is sufficient to make a recognizable clinical group. The pain was typical of cardiac ischemia in site, radiation and quality but differed from classical angina of effort in that there was a crescendo nature in the occurrence of symptoms, the attacks were more prolonged, and there was an inconstant relation of the pain to effort. It was considered that this prodromal pain lay in the ill-defined intermediate state between angina of effort and myocardial infarction, a state that has been variously called "coronary failure"[13], "acute coronary insufficiency"[14], "intermediate coronary syndrome"[15] and "slight coronary attacks"[16]. This clinical syndrome has been superbly described by Wood[17]: "The onset is usually acute or subacute: from a state of normal or relatively good health, the patient suddenly finds himself unable to walk more than a few yards without pain, and may have prolonged attacks of angina at rest, particularly after food and when he lies flat: but the pain is still relieved by trinitrin, there is no fever, leukocytosis, elevation of the sedimentation rate or increased transaminase activity, the blood pressure does not fall, there is no pericardial friction or other clinical evidence of cardiac infarction, and the electrocardiogram shows nothing more than the ischemic depression of the RS-T segment in left ventricular surface leads or their equivalents." The pathological basis of the syndrome is no doubt variable, but since it commonly develops rather abruptly, it is reasonable to attribute it to coronary thrombosis, but without accompanying myocardial infarction. The outcome of the state is also variable: the patient may return to normal

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health, may proceed to or continue a long history of angina of effort, or may go on to myocardial infarction. The relative incidence of these three modes of termination is not easily obtainable in a hospital series, since few of those who do not suffer from infarction are referred to hospital. From observations of the present study carried out in home, office and hospital, it is apparent that these attacks are more significant and dangerous than has been commonly realized.

The fatality rate in patients with prodromal symptoms was 15 per cent in Mounsey's series, and 34 per cent and 43 per cent in Sampson and Eliaser's and Yater's series respectively.

Dressler[18] has stressed that myocardial infarction may present merely as angina pectoris of effort. However, not infrequently myocardial infarction is preceded by an intensification of a previous angina of effort[1, 9]. As the pathologic basis[13] of angina of effort is frequently an occlusion of one or more major branches of the coronary artery, the sudden increase in symptoms usually means further narrowing or thrombosis in remaining vessels.

In a patient who has had a previous infarct and who has been subsequently pain-free, the recurrence of pain is particularly ominous. In such patients with known coronary disease, a more or less abrupt recurrence of pain indicates a sudden increase in the occlusive disease, usually on a basis of further thrombosis. In this situation it is reasonable to anticipate an increased incidence of infarction.

On the basis of these considerations and from observations on the present series, it is suggested that the syndrome of impending myocardial infarction has three common presentations[5]:

1. Onset of ischemic cardiac pain in a patient previously free of symptoms. Usually the patient experiences repeated bouts of spontaneously occurring pain lasting from 15 to 30 minutes or longer, without clinical, electrocardiographic or laboratory evidence of infarction. Less commonly, it may take the form of a rapidly progressive angina of effort. Whether the pain be at rest or with exertion, it occurs oftener, lasts longer, and becomes more severe over the course of a few days or weeks.

2. Intensification of angina of effort in a patient with previous angina of several months or years duration. Usually there is an abrupt change in the pattern of the chronic symptoms: pain occurs oftener, with less provocation, lasts longer and is more severe.

3. Recurrence of pain, at rest or on slight provocation, in a patient who has been pain-free ever since a previous myocardial infarction.

This classification is somewhat similar to that of Denham[19] based on observations made during a study of the acute phese of myocardial infarction in 920 patients[20].

It is apparent that the recognition of impending myocardial infarction depends on the occurrence of pain in one of the above forms. It may be that there are other symptoms which may herald the approach of myocardial infarction, but none other than pain have been found consistent or reliable. Where ischemia is not productive of ischemic pain there may well be no warning that infarction is threatening.

At this point it should be noted that patients presenting with the symptomatology of impending infarction are to be distinguished from "potential" or recurrent infarctions of the type described by Nichol[21] and others[22, 23]. In this latter group, patients with previous infarctions are placed on long term anticoagulant therapy to prevent further infarction. In the series here presented, in group 3 the indication was the recurrence of pain rather than the mere fact of previous infarction.

As a rule diagnosis is not difficult; the first consideration is to decide whether or not the patient's pain is due to cardiac ischemia. If it is, it is then necessary to be sure whether or not infarction is already present. If infarction is not present, and the pattern of the pain follows one of the three presentations already described, the diagnosis of impending infarction is likely. There have been encountered only two circumstances where progressive intensification of a chronic angina pectoris mimicked impending infarction: patients rather rapidly developing anemia, and a few patients to whom thyroid analogues were given in an effort to reduce hypercholesterolemia.

In some instances, at the onset of symptoms there was doubt regarding the diagnosis, but in these cases treatment was started in any case. After a period of observation had enabled a diagnosis other than impending infarction to be established, such cases were eliminated from the series. It must be constantly remembered that accurate diagnosis of impending infarction can sometimes be made only in retrospect but treatment must be initiated at the outset of a suspicious assembly of symptoms. Also, after some days of observation, it was apparent that a few cases had in fact infarcted at the time of presentation. These cases also were eliminated from the study.

Whenever a patient is suspected of having impending myocardial infarction, the electrocardiogram may provide helpful confirmatory evidence. The changes consist of primary T wave abnormalities or ST depressions. Such alterations are particularly helpful if electrocardiograms taken before the onset of pain are available for comparison. However it must be strongly stressed that the clinical diagnosis (on the basis of pain) must be adhered to and acted upon even if the electrocardiogram is normal. Unfortunately it has been an all too common experience to have patients report to a physician because of pain, have an electrocardiogram done and be told that it is normal, be thoroughly reassured, and then die suddenly a short time later. This has tended to detract from the

reputation of the electrocardiographic method as well as that of the physician. Even electrocardiograms done after exertion may be negative in the prodromal stage of myocardial infarction. In the experience here reported it has been frequently observed that serial electrocardiograms, taken over a period of several days at the onset of treatment for impending infarction, may show transitory but conclusive evidence of ischemia. It is obvious that to wait until electrocardiographic changes are incontrovertible is to waste precious time and may permit a preventable infarction to occur.

Treatment

Commencing early in 1949, all patients who presented with symptoms falling into any of the three categories of threatened infarction were diagnosed as impending myocardial infarction and immediate hospitalization for anticoagulant treatment and rest was advised. By December 1957, this diagnosis and recommendation had been made in 100 patients. In 85 of the 100 patients this recommendation was carried out; in the remaining 15 patients it was not. The latter patients therefore serve as "control" subjects. In nine of these "controls," the patients felt they could not take the time to undergo the proposed treatment or were not sufficiently impressed with the seriousness of their symptoms to heed the advice. These patients were encountered throughout all years of the study. The remaining six "control" subjects accepted the recommendation but as hospital beds were not available they were forced to remain on hospital waiting lists. These patients were all encountered in the earlier years of the series.

In the first years of the study patients were admitted to hospital as soon as possible after diagnosis, for treatment with anticoagulants. More recently, in some cases, anticoagulants have been administered in the office or home, pending admission to hospital. In addition to oral anticoagulants, in patients with rapid progression of symptoms, intravenous heparin was given in a dose of 50 mg. intravenously every four hours until prothrombin activity reached a therapeutic level. Of the total, 21 patients received heparin, the remainder received oral preparations only. From 1949 to 1951 the oral anticoagulant used was bishydroxycoumarin (Dicumarol);* subsequent to this the usual preparation was phenylindanedione (Danilone). Later as part of an investigation on the effect of oral anticoagulants on serum lipids, ethyl biscoumacetate (Tromexan) and acenocoumarin (Sintrom) were also used. In the 85 cases that received anticoagulants, Dicumarol was given to 8 patients, Sintrom to 4 patients, Tromexan to 1, and the remaining 72 were given Danilone.

After admission to hospital, patients received a complete physical examination, a 12 lead electrocardiogram, and roentgen examination of the chest. Routine laboratory investigation included complete blood count, Kahn test, estimation of sedimentation rate, fasting blood sugar and serum cholesterol. Electrocardiograms and sedimentation rates were repeated several times during the first few days, and subsequently as indicated by symptoms; they were again performed prior to discharge from hospital, usually two to four weeks later. Serum transaminase and other enzymes were measured in more recent cases.

Patients were encouraged to remain in bed, but often with bathroom privileges, until therapeutic anticoagulation was achieved, and until no longer subject to pain. They then became ambulant. When estimations of prothrombin activity stabilized in the therapeutic range and the maintenance dose of anticoagulant had been determined, patients were allowed home. Re-examinations were carried out at intervals of one to three months, or as clinically required.

Prothrombin activity was estimated at the onset of treatment and daily thereafter while patients were in hospital. After discharge from hospital it was estimated at weekly and later at two-weekly intervals. The prothrombin activity was estimated by the one-stage method of Quick, normal control value being 12 to 15 seconds. The upper and lower limits of the therapeutic range were considered to be 25 to 50 seconds (35 per cent and 17 per cent) respectively.

It soon became apparent that there was considerable advantage in securing prompt control of prothrombin activity with oral anticoagulants, thus permitting earlier discontinuance of intravenous injections of heparin. It had been noted that with the usually recommended doses of Danilone, several days often elapsed before the therapeutic range was reached. Accordingly a study[24] of optimum dosage to achieve rapid effect was undertaken. It was found that with larger doses, (e.g. 500-600 mg. in the first 24 hours) a more rapid control could be safely effected. These larger doses were not used in patients over the age of 65 or in patients with any evidence of congestive heart failure. In the case of Tromexan, Dicumarol and Sintrom, standard initiating and maintenance doses were used.

Clinical Features of the First Hundred Patients

Of the first 100 patients, 82 were males and 18 were females. Age ranged from 31 years to 77 years and averaged 57 years. The group thus exhibited the sex and age distribution characteristic of coronary disease in general. The 15 "control" patients did not differ in these respects from the 85 patients who were treated with anticoagulants. Details are given elsewhere[5].

Presenting symptoms at the time of diagnosis are shown in Table 1. Patients in the "control" group presented in a manner comparable to the treated

*For simplicity, the trade names of these compounds will be used in the remainder of this discussion.

group. The largest group consists of 45 patients who described the onset of characteristic cardiac pain which they had never had before. In this group a few patients began as angina of effort which progressed rapidly, but in all cases one or more episodes of pain at rest had occurred before the diagnosis was made. Duration of symptoms prior to inclusion in the series varied from one day to five months, with an average of 16 days. Significantly, in 15 patients the duration of symptoms was one day or less.

Table 1
Presenting Symptoms in Impending Myocardial Infarction

PRESENTATION:	Onset of progressive cardiac pain for first time.	Intensification of chronic angina of effort.	Recurrence of pain in patient with previous infarction.	TOTAL
Duration:				
Average days	16	13	7	
Range	1 day to 5 months	1 day to 5 months	1 day to 1 month	
Total cases	45	30	25	100
Anticoagulant	38 (45%)	24 (28%)	23 (27%)	85
"Control"	7 (47%)	6 (40%)	2 (13%)	15

The second most common mode of presentation was that of a rapidly progressive intensification of pre-existing angina of effort. This occurred in 30 patients. In these patients angina had been present from 2 months to 15 years with an average duration of 28 months. The period of intensification of symptoms varied from one day to five months and averaged 13 days.

The third group consisted of 25 patients with previous myocardial infarction in whom cardiac pain recurred after a pain-free interval of weeks, months or years. The interval between the old infarction and the recurrence of fresh ischemic pain ranged from 1 month to 10 years and averaged 23 months. The duration of the new premonitory symptoms of an additional impending infarction ranged from 1 day to 1 month and averaged 7 days. These patients, having previously experienced an episode of infarction, reported the recurrence of pain much sooner than did the other two groups.

Of the 100 patients, 34 were obese, 20 had persistent diastolic hypertension, and 5 were diabetic. Incidence of these conditions was not significantly different in the treated and "control" groups.

Electrocardiograms were taken on all patients at the time diagnosis was established. In the 25 patients with known previous infarction, the old infarct was recognizable in 24, the remaining record showed marked left ventricular hypertrophy with ST depression. Comparison with previous electrocardiograms indicated the presence of recent ischemia in 13 of the 24 patients, (52 per cent).

In 75 patients without known previous infarctions, 13 patients (17 per cent) had normal records, 58 patients (77 per cent) had evidence of ischemia, and the remaining 4 showed left ventricular hypertrophy. Eleven of the 13 normal records remained normal and 35 of the 58 ischemic records improved.

In the "control" patients, 4 (20 per cent) had normal tracings, 8 (53 per cent) showed ischemia, 2 (13 per cent) revealed old infarcts with recent ischemia and 1 indicated left ventricular hypertrophy.

Results of Treatment

In assessing the effect of treatment of impending infarction it is necessary to take into account the duration of treatment and its relationship to the time at which symptoms of "impending" are first manifest. Accordingly the first six weeks after onset of symptoms have been arbitrarily considered to be the "acute phase," the period from seven weeks to six months the "chronic phase" and from six months onward the "late phase." Table 2 shows the outcome of the 85 treated patients compared to the 15 "control" patients in each of these phases[5].

Table 2
Outcome in Patients Receiving Anticoagulant and in "Controls"

	Entire Series	"CONTROLS"		ANTICOAGULANT		
		Acute Phase 0 - 6 wks.	Chronic Phase 7 wks. - 6 mos.	Acute Phase 0 - 6 wks.	Chronic Phase 7 wks. - 6 mos.	Late Phase Over 6 mos.
No. of Patients	100	15	3	85	80	57
No. of Infarcts	42**(42%)	12	2	2*	3	10
No. of Deaths	24**(24%)	9	2	0	2	7

* one with prothrombin time above therapeutic range.
** includes those occurring after anticoagulants discontinued.

In the 15 "control" patients it is almost incredible to find that 14 infarcted. Of these, 11 were fatal and 3 were non-fatal. The three non-fatal infarcts occurred from three to four days after diagnosis of impending infarction had been made. The 11 fatal infarctions occurred from three to 92 days (average 20 days) after diagnosis. However, excluding two patients who survived 56 days and 92 days respectively, the remaining nine fatalities occurred on an average of eight days after diagnosis, (range three to 19 days). Thus 12 patients infarcted, nine of them fatally, during the "acute phase." Two of the three patients who reached the "chronic phase" then infarcted fatally.

In none of these patients was infarction associated with undue effort or emotion; thus it does not seem reasonable to attribute these deaths to lack of rest alone. One can only speculate as to the probable outcome had anticoagulants been given, but in the light of results in treated patients, now to be presented, it seems likely that more would have survived.

Of the 85 patients who received anticoagulants during the "acute phase," only two had infarcts and neither of these was fatal. One of them occurred when the prothrombin time was temporarily above the therapeutic range. In five patients, anticoagulants were discontinued during this phase. Of

the 80 patients carried on treatment to the "chronic phase," three infarcted, two being fatal. In the "late phase," reached by 57 treated patients, 10 of them suffered infarctions and seven of these were fatal.

The benefits of anticoagulants in the "acute" and "chronic" phases appears substantial. Although the data is not susceptible to statistical analysis, the striking difference in outcome between the treated and "control" patients strongly suggests that anticoagulants exert a protective influence in the state of impending infarction. The incidence of fatal infarction and sudden death in the "chronic phase" appears to be a matter of the influence of long term anticoagulants in patients with chronic coronary disease, rather than in the more restricted state of "impending infarction."

Ideally, one would prefer to have a large series with alternate patients serving as controls. In the present series the "controls" were selected in part by themselves, and in part by the chance unavailability of hospital accommodation. However, there was striking similarity to the treated groups in respect to age, sex, mode of presentation, duration of syndrome and electrocardiographic findings.

Complications of Treatment

As in the case of anticoagulants used for other purposes, the main complication in this series was hemorrhage. During a total of 6,404 patient-weeks of therapy, hemorrhage occurred on 37 occasions. In 15 patients the bleeding consisted of hematuria and in six patients epistaxis occurred. In 27 patients the hemorrhage was of minor degree and did not necessitate more than simple local measures and the temporary withholding of further anticoagulants. In 10 patients the bleeding was considered of major proportions and necessitated hospital treatment; in six cases the source of this severe bleeding was from the gastrointestinal tract. In no case was death directly attributable to hemorrhage although in two instances hemorrhage necessitated the discontinuance of anticoagulants and this in turn was promptly followed by infarction which proved fatal.

In the second 100 patients (not yet analyzed in detail) two fatal cerebral hemorrhages occurred; in both instances bleeding occurred into areas of old cerebral softening.

Several unusual complications were encountered. One patient had a severe hemolytic reaction following intravenous vitamin K_1 given for bleeding due to excessive hypoprothrombinemia[25]. Another patient had a sensitivity reaction to Danilone but recovered promptly following prednisone[26]. Three patients developed intestinal obstruction associated with excessive hypoprothrombinemia[27].

Mode of Action of Anticoagulants

As the study progressed it became increasingly clear that anticoagulants were affecting the outcome favorably. The next problem was to investigate the mechanism of this benefit. Although it is ordinarily presumed that oral anticoagulants act only by the prevention of thrombosis, the possibility that they might act in some way on the underlying process of atherosclerosis must be considered. This idea was favored by the fact that the anticoagulant heparin has antilipemic properties. Although a causal relationship between elevated serum lipids and clinical atherosclerosis has not yet been unequivocally demonstrated, there is nevertheless sufficient evidence to suggest this possibility. There is therefore importance in determining whether or not the commonly used oral anticoagulants exert any influence on these processes other than the well known hypoprothrombinemic action. Accordingly, experiments were designed to determine what effect several oral anticoagulants had on serum lipids and on the heparin-activated clearing factor.

In atherosclerotic subjects, some of them with impending infarction, serum cholesterol, total serum lipids and B-lipoprotein were determined prior to initiation of treatment with Danilone, Sintrom or Tromexan. In the Danilone-treated group no significant change occurred in any of these serum lipids. In patients treated with Sintrom and Tromexan, elevations occurred in the serum cholesterol and total serum lipids which were maintained for at least 10 weeks but were back to pretreatment levels after 24 to 32 weeks of therapy[28]. The significance of these observations is not clear but it would appear that none of these oral anticoagulants produce any beneficial alteration in the lipids of atherosclerotic subjects.

During the past few years many studies of lipid metabolism and its derangements have been concerned with a clearing factor evoked in blood plasma by the in vivo injection of heparin. Hahn[29] in 1943 made the observation that administration of heparin clears the turbidity of alimentary lipemic plasma, a phenomenon now attributed to a plasma lipase which may be called heparin-activated clearing factor. Because of a possible relationship of this factor to atherosclerosis, the response of this substance in atherosclerotics treated with each of the three above oral anticoagulants was studied. It was found that none of them exerted any influence on heparin-induced clearing activity[30].

From these observations it appears that the benefits of anticoagulant therapy are not due to an effect on lipid metabolism or on clearing factor. Presumably the oral anticoagulants do act to prevent thrombosis, a process which is probably most often the basis of impending infarction. If such be the case, the benefit of anticoagulant therapy in the state of impending infarction is not surprising.

Program of Patient-Education

Although it required nearly nine years to obtain the first 100 patients with impending infarction, a second 100 patients was met within the next 2½ years. The greater frequency of the diagnosis is

no doubt due in part to the increasing number of cardiac patients seen by the authors, but a portion of the increase is also due to a program of education of patients, whereby all patients with coronary disease are instructed to report to the physician any appreciable change in the behaviour of their cardiac pain. In this way more patients come under medical observation before they have progressed to the stage of actual infarction. If the recommended preventative measures are of value, it is obvious that this program of patient-education is of importance. There is, of course, the disadvantage that the physician is frequently informed of insignificant pains, but after a few discussions with patients they soon learn which pains to report and which to ignore. In any case it is felt that the advantages of early reporting of pain have far outweighed the occasional annoyances occasioned by the method. This procedure might be crudely compared to that of having patients report potentially pre-malignant lesions to the physician before established cancer has occurred.

Discussion

Considering its potential importance, little attention has been paid to impending infarction. Perhaps this lack of interest has been due, until recently, to inability to significantly alter the outcome. With the demonstrated value of anticoagulants, particularly during the "acute phase" of impending infarction, increased effort to recognize and treat the condition may be forthcoming. Two substantial series, that of Nichol et al[31] in Miami, Florida, and that of Maurice et al[32] in Paris, France, will no doubt increase awareness of the syndrome.

Nicol et al[31] report on 318 patients with impending infarction treated with anticoagulants during a 10-year period. Only 21 patients (6.8 per cent) developed frank infarction (5 fatal) within 30 days. Of the remaining 297 patients, 267 did not develop infarction within 60 days while on anticoagulants, but the 30 patients who discontinued treatment within 60 days experienced an infarction rate of 56.6 per cent with 12 fatalities. Mortality in the total series over the 10-year interval was 33 per cent. These authors obviously feel, as we do, that prompt anticoagulant therapy is of value in the pre-infarction state. As two thirds of their patients had previous infarction, whereas only one quarter of our patients were in this category, there is probably considerable difference between the two series although both appear to have been benefitted.

Maurice et al[32] studied 108 patients with myocardial infarction and found that 39 per cent had premonitory symptoms varying from a few hours to a month or more. With this experience as a guide, 71 patients with premonitory symptoms were treated with anticoagulants. Two patients had non-fatal infarctions during treatment, but eight patients died of infarction one to 16 months after stopping treatment. Clinical features of their patients were similar to the present series, but more of them presented as an intensification of pre-existing angina of effort.

Because the period of prodromal symptoms is often short, there is urgency in achieving anticoagulant effect. Thus the more quickly acting oral anticoagulants have an advantage. The necessity for heparin at the initial stage has not been established but its use seems rational. It is noted that Maurice et al [32] used it in 46 of 71 patients. In the present series it was used in 21 of the 85 patients; in none of these did death or infarction occur during the "acute phase," but one patient, adequately controlled, died 20 weeks later.

Optimum duration of anticoagulant treatment in impending infarction is not established. It appears that benefit is considerable during the first six months after onset of symptoms. In many patients the persistence of symptoms, the presence of gross arterial disease, or past history of several thrombotic episodes, indicate that anticoagulants should be continued indefinitely.

The reported incidence of infarction (usually 30 per cent to 50 per cent) and of fatality (15 per cent to 43 per cent) in patients with prodromal symptoms has been mentioned. The reduction of both by use of anticoagulants in this series is impressive, both by comparison with a "control" series and with the expectations from published studies. Further support is afforded by results of anticoagulant therapy of impending infarction reported by several authors. Wood[1] treated 33 patients with "acute coronary insufficiency" with a result of two infarcts and no deaths: in 25 similar untreated cases there were 12 infarcts and five deaths. Nichol et al[33] recently reported 6 per cent mortality in 96 treated patients and 18 per cent mortality in 32 patients abandoning treatment. Maurice et al[32] observed only two infarctions to 71 patients. The similarity in these reports is persuasive.

The pathological basis of impending infarction is even less well understood than the mechanism of coronary occlusion itself. In those patients in whom premonitory symptoms develop abruptly, it seems likely that an acute change has occurred in the coronary circulation, whether it be thrombosis, subintimal hemorrhage or occlusion by a plaque. The incidence and role of subintimal hemorrhage in production of coronary occlusion is not agreed upon, but it is sometimes stated that its possible presence is a contraindication to the use of anticoagulants. From the beneficial effects of anticoagulants, noted in this and other series, it would appear that either subintimal hemorrhage is not aggravated by anticoagulants, or that secondary thrombosis in relation to the subintimal hemorrhage is prevented, or that it is not a common cause of infarction.

The mechanism causing death in patients with coronary atherosclerosis is often not clear even

Adrenergic Factors in Hypertension

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A general discussion of adrenergic factors in hypertension cannot be justified on the basis of recent important advances. Much of the information in this field was accumulated over a decade ago, and subsequent investigations have been limited by the relatively unpromising nature of the earlier findings, at least as they relate to an understanding of human essential hypertension. However, the subject is of importance because a major part of our current therapy of essential hypertension is directed toward control of these factors, and a clear appreciation of their importance is essential if we are to view the actions of and responses to many of the currently employed drugs in proper perspective.

Adrenergic factors in hypertension can be defined as those mechanisms involved in the maintenance of arterial pressure which operate via the release of adrenaline or noradrenaline. The term "neurogenic" is an acceptable synonym, as it is only the nerves releasing these substances as their chemical mediators which effectively constrict blood vessels or stimulate the myocardium. "Sympathoadrenal" also may be used interchangeably with adrenergic, because in most, but not necessarily all situations, the activity of sympathetic, adrenergic nerves and the release of adrenaline from the adrenal medulla occur together. For most of the present discussion it will be unnecessary to distinguish between the local release of noradrenaline at sympathetic nerve endings, and the release of adrenaline into the blood stream. However, it should be pointed out that most of the adrenergic control of vascular tone is exerted via noradrenaline and the sympathetic nerves, with only a minor contribution from circulating mediators[9].

Experimental neurogenic (adrenergic) hypertension can be induced by a variety of procedures, and has been known and studied for many years. Figure 1 illustrates the principal nervous pathways involved in the maintenance of blood pressure. Under normal conditions, the afferent pathways from the carotid sinus and aortic arch baroreceptor areas carry tonic impulses which depress the activity of the vasomotor centres. Consequently, section of these moderator nerves brings about a sustained elevation in blood pressure[25, 27]. It also is well known that a similar hypertension can be induced by direct effects on the central nervous system. An increase in sympathoadrenal activity and a consequent increase in blood pressure can be induced by electrical stimulation of or injury to the hypothalamus[29,45], and both acute and chronic increases in systemic arterial pressure may result from an increased intracranial pressure, at least in part because of the cerebral ischemia which results[11, 20, 24]. Man is known to respond in much the same way as do experimental animals to section of the buffer nerves[16] or to increased intracranial pressure[10]. However, elevation of blood pressure on these bases is relatively rare, and, obviously, is unrelated to the usual clinical hypertension.

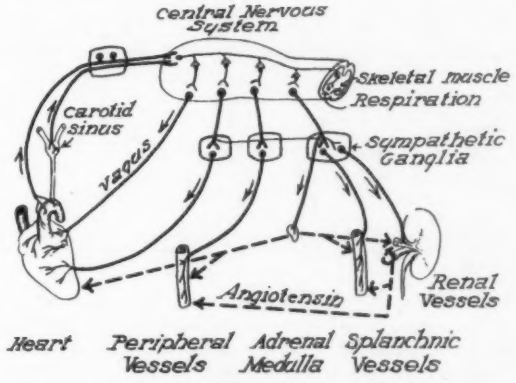

Figure 1

Diagrammatic representation of the principal nervous and humoral pathways involved in the maintenance of systemic arterial pressure. Solid lines depict nervous pathways and broken lines humoral agents.

A more important, but much more nebulous, involvement of nervous factors in clinical hypertension is suggested by the many clinical observations which indicate that the central nervous system may in some way influence the development and maintenance of an elevated pressure. It has long been recognized that stressful situations may induce marked increases in both systolic and diastolic pressures which persist for varying periods of time[13, 19], and that rest and freedom from daily stress, such as may be associated with a holiday or a short period of hospitalization, have a salutary effect on the pressure of many hypertensive patients.

In spite of many observations which suggest that central factors may modify significantly the blood pressure in patients with essential hypertension and the fact that these central influences probably are mediated through adrenergic nerves, it is now quite clear that the elevated pressure in essential hypertension is not maintained primarily by adrenergic factors. Some of the more prominent features of neurogenic and essential hypertension are listed in table 1. A review of these characteristics indicates that human essential hypertension and uncomplicated neurogenic hypertension have

no doubt due in part to the increasing number of cardiac patients seen by the authors, but a portion of the increase is also due to a program of education of patients, whereby all patients with coronary disease are instructed to report to the physician any appreciable change in the behaviour of their cardiac pain. In this way more patients come under medical observation before they have progressed to the stage of actual infarction. If the recommended preventative measures are of value, it is obvious that this program of patient-education is of importance. There is, of course, the disadvantage that the physician is frequently informed of insignificant pains, but after a few discussions with patients they soon learn which pains to report and which to ignore. In any case it is felt that the advantages of early reporting of pain have far outweighed the occasional annoyances occasioned by the method. This procedure might be crudely compared to that of having patients report potentially pre-malignant lesions to the physician before established cancer has occurred.

Discussion

Considering its potential importance, little attention has been paid to impending infarction. Perhaps this lack of interest has been due, until recently, to inability to significantly alter the outcome. With the demonstrated value of anticoagulants, particularly during the "acute phase" of impending infarction, increased effort to recognize and treat the condition may be forthcoming. Two substantial series, that of Nichol et al[31] in Miami, Florida, and that of Maurice et al[32] in Paris, France, will no doubt increase awareness of the syndrome.

Nicol et al[31] report on 318 patients with impending infarction treated with anticoagulants during a 10-year period. Only 21 patients (6.8 per cent) developed frank infarction (5 fatal) within 30 days. Of the remaining 297 patients, 267 did not develop infarction within 60 days while on anticoagulants, but the 30 patients who discontinued treatment within 60 days experienced an infarction rate of 56.6 per cent with 12 fatalities. Mortality in the total series over the 10-year interval was 33 per cent. These authors obviously feel, as we do, that prompt anticoagulant therapy is of value in the pre-infarction state. As two thirds of their patients had previous infarction, whereas only one quarter of our patients were in this category, there is probably considerable difference between the two series although both appear to have been benefitted.

Maurice et al[32] studied 108 patients with myocardial infarction and found that 39 per cent had premonitory symptoms varying from a few hours to a month or more. With this experience as a guide, 71 patients with premonitory symptoms were treated with anticoagulants. Two patients had non-fatal infarctions during treatment, but eight patients died of infarction one to 16 months after stopping treatment. Clinical features of their patients were similar to the present series, but more of them presented as an intensification of pre-existing angina of effort.

Because the period of prodromal symptoms is often short, there is urgency in achieving anticoagulant effect. Thus the more quickly acting oral anticoagulants have an advantage. The necessity for heparin at the initial stage has not been established but its use seems rational. It is noted that Maurice et al [32] used it in 46 of 71 patients. In the present series it was used in 21 of the 85 patients; in none of these did death or infarction occur during the "acute phase," but one patient, adequately controlled, died 20 weeks later.

Optimum duration of anticoagulant treatment in impending infarction is not established. It appears that benefit is considerable during the first six months after onset of symptoms. In many patients the persistence of symptoms, the presence of gross arterial disease, or past history of several thrombotic episodes, indicate that anticoagulants should be continued indefinitely.

The reported incidence of infarction (usually 30 per cent to 50 per cent) and of fatality (15 per cent to 43 per cent) in patients with prodromal symptoms has been mentioned. The reduction of both by use of anticoagulants in this series is impressive, both by comparison with a "control" series and with the expectations from published studies. Further support is afforded by results of anticoagulant therapy of impending infarction reported by several authors. Wood[1] treated 33 patients with "acute coronary insufficiency" with a result of two infarcts and no deaths: in 25 similar untreated cases there were 12 infarcts and five deaths. Nichol et al[33] recently reported 6 per cent mortality in 96 treated patients and 18 per cent mortality in 32 patients abandoning treatment. Maurice et al[32] observed only two infarctions to 71 patients. The similarity in these reports is persuasive.

The pathological basis of impending infarction is even less well understood than the mechanism of coronary occlusion itself. In those patients in whom premonitory symptoms develop abruptly, it seems likely that an acute change has occurred in the coronary circulation, whether it be thrombosis, subintimal hemorrhage or occlusion by a plaque. The incidence and role of subintimal hemorrhage in production of coronary occlusion is not agreed upon, but it is sometimes stated that its possible presence is a contraindication to the use of anticoagulants. From the beneficial effects of anticoagulants, noted in this and other series, it would appear that either subintimal hemorrhage is not aggravated by anticoagulants, or that secondary thrombosis in relation to the subintimal hemorrhage is prevented, or that it is not a common cause of infarction.

The mechanism causing death in patients with coronary atherosclerosis is often not clear even

Adrenergic Factors in Hypertension

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A general discussion of adrenergic factors in hypertension cannot be justified on the basis of recent important advances. Much of the information in this field was accumulated over a decade ago, and subsequent investigations have been limited by the relatively unpromising nature of the earlier findings, at least as they relate to an understanding of human essential hypertension. However, the subject is of importance because a major part of our current therapy of essential hypertension is directed toward control of these factors, and a clear appreciation of their importance is essential if we are to view the actions of and responses to many of the currently employed drugs in proper perspective.

Adrenergic factors in hypertension can be defined as those mechanisms involved in the maintenance of arterial pressure which operate via the release of adrenaline or noradrenaline. The term "neurogenic" is an acceptable synonym, as it is only the nerves releasing these substances as their chemical mediators which effectively constrict blood vessels or stimulate the myocardium. "Sympathoadrenal" also may be used interchangeably with adrenergic, because in most, but not necessarily all situations, the activity of sympathetic, adrenergic nerves and the release of adrenaline from the adrenal medulla occur together. For most of the present discussion it will be unnecessary to distinguish between the local release of noradrenaline at sympathetic nerve endings, and the release of adrenaline into the blood stream. However, it should be pointed out that most of the adrenergic control of vascular tone is exerted via noradrenaline and the sympathetic nerves, with only a minor contribution from circulating mediators[9].

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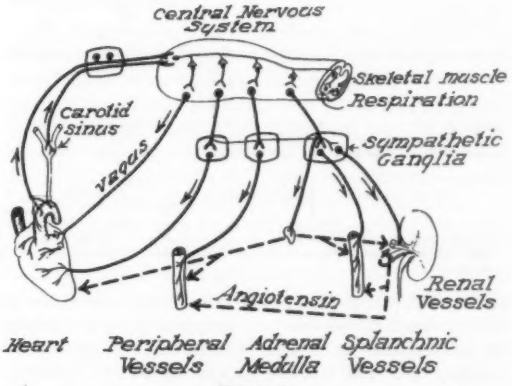

Figure 1

Diagrammatic representation of the principal nervous and humoral pathways involved in the maintenance of systemic arterial pressure. Solid lines depict nervous pathways and broken lines humoral agents.

A more important, but much more nebulous, involvement of nervous factors in clinical hypertension is suggested by the many clinical observations which indicate that the central nervous system may in some way influence the development and maintenance of an elevated pressure. It has long been recognized that stressful situations may induce marked increases in both systolic and diastolic pressures which persist for varying periods of time[13, 19], and that rest and freedom from daily stress, such as may be associated with a holiday or a short period of hospitalization, have a salutary effect on the pressure of many hypertensive patients.

In spite of many observations which suggest that central factors may modify significantly the blood pressure in patients with essential hypertension and the fact that these central influences probably are mediated through adrenergic nerves, it is now quite clear that the elevated pressure in essential hypertension is not maintained primarily by adrenergic factors. Some of the more prominent features of neurogenic and essential hypertension are listed in table 1. A review of these characteristics indicates that human essential hypertension and uncomplicated neurogenic hypertension have

Table I

Cardiovascular Characteristics of Various Types of Hypertension

Indices \ Mechanisms	Neurogenic (Adrenergic) Hypertension	"Essential" Hypertension	Adrenaline Infusion*	Noradrenaline Infusion*
Pulse rate	↑	N	↑	N or ↓
Cardiac output	↑	N	↑	N or ↓
Peripheral resistance	N	↑	↓	↑
Blood flow in extremities	↑	N	↑	↓
Pressure fluctuations	Marked	Marked early Limited late	Controlled	Controlled
Response to sympathectomy or to chemical blockade	Complete and uniform	Partial and variable	Complete and uniform	Nearly complete and uniform

N = normal; ↑ = increased; ↓ = decreased.

* Characteristics depend on the rate of infusion. Those presented here are for infusion rates which do not cause excessive discomfort in man.

little in common. Hemodynamic characteristics of the elevated blood pressure induced by the infusion of adrenaline or noradrenaline are included for comparison. The overall effects of the two mediators are very different. Infusion of noradrenaline does induce hemodynamic changes quite comparable to those observed in essential hypertension, but this similarity does not appear to have etiological significance. Hypertension with these same characteristics may be duplicated by the infusion of any agent producing generalized peripheral vasoconstriction which predominates over cardiac stimulation.

In contrast to the elevated blood pressure induced by adrenergic factors, renal and sodium-corticoid hypertensions have many characteristics in common with human essential hypertension. It is impossible to discuss these other types of experimental hypertension in detail here, but they are mentioned because of the still unproved possibility that some interaction between adrenergic mechanisms and these other possible etiological factors may explain the clinically observed participation of the central nervous system in essential hypertension, which obviously is not predominantly adrenergic in nature.

Renal vasoconstriction, with consequent alteration of renal hemodynamics and the release of angiotensin into the blood stream is depicted in figure 1 as a possible component of the response to activation of the sympathetic system. Neurogenic renal vasoconstriction obviously is not a major factor in the development of classical experimental neurogenic hypertension. Renal denervation causes only a very limited fall in the blood pressure of neurogenic hypertensive animals[21], and prior nephrectomy does not alter the pressor response to section of the buffer nerves[43].

Indirect arguments for the participation of neurogenic factors in the later stages of renal hypertension[10] are unconvincing (c.f.[37, 39]). However, it has been shown that a sustained hypertension can be produced by reflex neurogenic renal vasoconstriction after the sympathetic innervation of all other body structures has been removed[22], or by prolonged electrical stimulation of the renal nerves[33], and the possibility that neurogenic renal vasoconstriction ultimately may induce a hypertension sustained by nonneurogenic renal factors deserves further investigation.

One of the distinguishing characteristics of uncomplicated neurogenic hypertension is its dramatic response to surgical sympathectomy or to chemical blockade of the sympathetic nervous system. Sympathectomy results in an immediate reduction of the blood pressure to normal or to subnormal levels[21, 26], and moderator nerve section or increased intercranial pressure usually fails to increase the blood pressure in sympathectomized animals[15, 21]. Limited, slow elevations in pressure induced by these procedures in "completely sympathectomized" animals appear to be explicable on the basis of sympathetic fibres which do not pass through the paravertebral sympathetic chains[6]. Similarly, consistent and persistent lowering of the blood pressure to normotensive levels can be induced in neurogenic hypertensive animals by any of the even moderately effective adrenergic or ganglionic blocking agents[3, 29, 30]. This dramatic response contrasts sharply with the variable and often limited reduction in blood pressure seen in patients with essential hypertension and in animals with renal or corticoid-induced hypertension.

Although it is clear that the elevated blood pressure in essential hypertension is maintained by mechanisms which do not involve primary participation of adrenergic nerves, evaluation of sympathetic nervous system activity in this condition is of considerable importance. The carotid and aortic baroreceptor reflexes normally operate to keep the blood pressure within a relatively narrow range, inducing vasodilatation via a decrease in sympathetic tone when the blood pressure tends to rise and causing increased vasoconstriction when the blood pressure tends to fall. Indeed, these reflexes are so sensitive to small pressure changes and so efficient in causing the appropriate vascular adjustments that the normal animal or human may adjust to very wide fluctuations in cardiac output without any change in blood pressure which can be detected by the usual sphygmomanometer techniques. It has been observed repeatedly in both animals and in man that the operation of these baroreceptor reflexes is largely independent of the

etiological factors tending to alter the blood pressure, and that a marked increase in pressure occurs only after sympathetic vasomotor tone has been largely eliminated and further reflex vasodilatation is therefore impossible.

However, the results of many studies of sympathetic vasomotor tone in patients with essential or renal hypertension agree that this is not significantly different from that found in normotensive individuals[16, 17, 42]. It appears that the buffer reflexes of the hypertensive operate in the range of his usual blood pressure in much the same way as those of a normotensive individual, although the "norm" to which they tend to return the blood pressure may be much higher. Thus, the vasomotor reflexes of the patient with essential hypertension have been reset to operate from a new baseline. It has been suggested that such "resetting" may be the primary factor in the development of clinical hypertension[28]. However, the many important differences between the neurogenic hypertension which this would induce and human essential hypertension, with respect to both hemodynamic criteria and responses to hypotensive drugs, make such an hypothesis untenable.

Changes in the setting of baroreceptor reflexes during the development of a chronically elevated blood pressure have been studied in some detail in dogs with renal hypertension[31, 34]. As the blood pressure increases in response to the altered renal hemodynamics, the level at which the carotid sinus responds to induce vasodilatation also increases, but at a somewhat slower rate. The baroreceptor reflexes thus act to slow the development of the hypertension. However, after several months, adaptation to the new "basal" pressure is complete, and the reflexes are involved only in buffering short-term changes in pressure. A similar pattern is seen during the return to normotension following release of renal artery constriction or removal of an involved kidney. Again the rather slow resetting appears to oppose the change, in this case tending to keep the blood pressure elevated. Direct observations of impulse traffic in the sinus nerve in response to intralumenal pressure changes in the carotid sinus indicate that resetting occurs in the pressure sensitive elements themselves[34]. However, the nature of the changes involved, which are too slow to be attributed to fatigue or accommodation in the usual sense, is entirely unknown.

It is possible that delayed resetting of the baroreceptor mechanism is involved in the relatively slow return of the blood pressure to hypertensive levels occasionally seen when drug therapy is withdrawn or reduced in patients who have been maintained at or near normotensive levels for considerable periods of time. However, a more important consideration from the standpoint of therapy is the fact that the vasomotor reflexes can actively regulate the blood pressure in the hypertensive range, and consequently, that the blood vessels of patients with essential hypertension are under a significant degree of adrenergic vasomotor tone. It is the presence of this adrenergic tone which makes possible a hypotensive response to the many drugs which act to decrease sympathetic vasoconstrictor tone (table 2).

A major problem in the use of such drugs and surgical sympathectomy is the highly variable and unpredictable responses obtained. Some patients react with a prompt and well-sustained reduction

Table II
Agents Reducing Sympathetic Vasoconstrictor Tone

Type of Agent	Examples	Locus of Action	Major Desirable Characteristics	Major Undesirable Characteristics
Veratrum Alkaloids	Protoveratrines	Reflex via baroreceptors	Bradycardia No postural hypotension	Low therapeutic margin Nausea and vomiting
Ergot Alkaloids	Hydergine®	Primarily on central nervous system	Bradycardia Limited postural hypotension	Low therapeutic margin Nausea and vomiting
Rauwolfia Alkaloids	Reserpine	Depletes adrenergic mediators in sympathetic nerves and adrenal medulla	Bradycardia Limited postural hypotension	Sedation, psychic depression, nightmares, increased gastrointestinal secretion and motility, Parkinsonism
Ganglionic Blocking Agents	Hexamethonium Mecamylamine Inversine®	Sympathetic and parasympathetic ganglia	Complete inhibition of sympathetic tone Limited tachycardia	Postural hypotension Blockade of parasympathetic ganglia: constipation, ileus, cycloplegia, urinary retention, impotence, etc.
Inhibitors of mediator release	Bretylium Darenthin®	Prevents release of adrenergic mediators from sympathetic nerves and adrenal medulla	No effect on parasympathetic system No tachycardia	Postural hypotension
Adrenergic Blocking Agents	Phenoxybenzamine Dibenzyline®	Prevents vasoconstrictor responses to adrenergic mediators	No effect on parasympathetic system Complete inhibition of adrenergic vasoconstriction	Postural hypotension Tachycardia

in the blood pressure to essentially normal levels, whereas the blood pressure of others is largely or entirely refractory. A general inverse relationship between the "severity" of the hypertensive disease, not necessarily the same as the degree of elevation of the blood pressure, and the hypotensive response frequently is observed, but exceptions are extremely common. It often is said that the response to sympathectomy or to chemical inhibition of adrenergic vasoconstriction is proportional to the "neurogenic" component of the disease in a given patient. This point of view would appear superficially to have some logical basis. However, it never has been substantiated by independent observations, and becomes a meaningless circular argument in that a good response occurs in patients with a large "neurogenic" factor, for which the only evidence is the good response. This interpretation requires that the adrenergic vasoconstrictor tone in different hypertensive patients must vary from an insignificant level to a magnitude adequate to account for the entire abnormal elevation in blood pressure. However, as mentioned above, many observations on sympathetic reflexes and on adrenergically-mediated vasomotor tone indicate a fairly constant and relatively normal level of adrenergic vasomotor activity in patients with essential hypertension.

Another possible explanation for the highly variable hypotensive responses to inhibition of sympathetic vasoconstriction can be found in the poorly defined factors which regulate vascular tone in the absence of sympathetic control. It is well known that the smooth muscle of blood vessels can maintain a considerable tone on the basis of local and humoral factors after sympathectomy or in the presence of chemical blockage of sympathetic activity. Nonadrenergic vascular tone probably is present at all times, to varying degrees in different individuals, and it tends to increase in magnitude and importance after sympathetic control is eliminated. Expressions of its substitution for sympathetic activity are seen in the very limited fall in blood pressure which occurs when the sympathetics are blocked relatively slowly in recumbent, normotensive individuals[18], in the somewhat sluggish, but important nonneurogenic adjustments to postural changes which develop over several days or weeks after chemical blockade of the sympathetic nervous system or almost complete surgical sympathectomy[23], and in the return of blood flow in a sympathectomized extremity to near preoperative levels long before possible regeneration of the sympathetic nerves[1].

The small peripheral vessels in patients with essential hypertension have been shown to have a significantly elevated tone, measured as critical opening pressure, which persists after acute local anesthetic block of their nerve supply[17], and it has been suggested that this increased tension in the vascular wall may be a simple mechanical result of morphological changes[14]. Thus, it appears quite possible that the magnitude of the fall in pressure after the administration of an agent which blocks sympathetic nervous system activity is regulated primarily by the level at which nonnervous, nonadrenergic factors can maintain the blood pressure without assistance from the sympathetic nervous system.

Another important expression of the nonsympathetic factors controlling vascular tone is seen in the development of "tolerance" to the effects of most hypotensive agents. It is clear that true pharmacological tolerance or resistance to the characteristic actions of at least some of these agents can develop[35]. However, much of the resistance to the net hypotensive effect appears to be nonspecific and to extend to agents with entirely different structures and mechanisms of action[12]. Thus it appears that a major factor in the development of resistance to agents inhibiting sympathetic nervous system activity is dependent on the development of compensatory mechanisms which allow the maintenance of a normal or even considerably elevated vascular tone without the intervention of the sympathetic nervous system.

Drugs which Reduce Adrenergic Vasoconstrictor Tone

Various types of clinically employed hypotensive agents which act by decreasing adrenergic vasoconstriction are listed in Table 2. Although their final effects on adrenergic vasoconstrictor tone may be similar, their loci and mechanisms of action, and consequently their clinical characteristics and side effects, vary widely. Each of these groups, and individual agents within them, have many pharmacological properties of importance to proper utilization. However, only a few major characteristics can be mentioned here.

Veratrum alkaloids

Many alkaloids obtained from various species of Veratrum act by inducing a repetitive discharge of many types of excitatory cells. However, certain visceral afferent (sensory) nerves are particularly sensitive to this action and are the only structures affected significantly by doses employed clinically. Rapid intravenous administration of an agent such as protoveratrine can activate sensory fibres arising along the distribution of the left coronary arteries, causing transient reflex bradycardia and peripheral vasodilation (the Bezold - Jarisch reflex). However, a much more important and persistent action of the veratrum alkaloids is sensitization of baroreceptors such as those of the carotid sinus[4]. Because the receptors now fire repetitively in response to a stimulus which would normally cause a more limited discharge, this action has the effect of setting the baroreceptors to a lower pressure. This is a very desirable mechanism of hypotensive action in that the fall in blood pressure is associated with a relative

bradycardia, and postural hypotension does not develop. However, receptors in the nodose ganglion of the vagus are only slightly less sensitive than the baroreceptors to the action of the veratrum alkaloids, and their activation leads to nausea and vomiting. Consequently, the margin between effective and nauseant doses is narrow, particularly with chronic administration. All of the many alkaloids studied appear to be similar in this regard.

Ergot alkaloids

The naturally occurring ergot alkaloids have a direct vasoconstrictor action which is much too strong for them to be used as hypotensive agents. However, their dihydro derivatives are much weaker vasoconstrictors and Hydergine[R], a mixture of dihydroergocornine, dihydroergocristine and dihydroergokryptine, has significant vasodilator and hypotensive effects. This preparation has potent adrenergic blocking properties, but in doses tolerated by man, the hypotensive action appears to be due entirely to a central depression of vasomotor tone[32, 36]. A combination of decreased sympathetic and increased vagal tone leads to a desirable bradycardia. Because compensatory reflexes still can operate to a considerable degree, postural hypotension is minimal. Unfortunately, these desirable characteristics are offset by a potent stimulation of the chemoreceptor trigger zone of the medulla, and there is little margin between the minimal hypotensive dose and that which produces nausea and vomiting. Because of this margin and the fact that the agent is poorly effective after oral administration, it has been little used as a hypotensive agent.

Rauwolfia alkaloids

These substances, of which reserpine is the best known, have prominent effects on the central nervous system, and in doses larger than those used in the treatment of hypertension, are effective tranquilizing agents in psychotic patients. Their hypotensive effect originally was attributed to an action on the central nervous system, but during the past few years data have accumulated which indicate that their major effect on blood pressure is due to depletion of the adrenergic mediator in sympathetic nerves[7, 8]. Related agents which do not deplete peripheral stores of adrenaline and noradrenaline are not hypotensive. The small doses commonly employed in the treatment of hypertension usually produce only a moderate decrease in blood pressure associated with bradycardia. Larger doses may produce a somewhat greater effect, but this is not enough to justify the considerable increase in side effects. Postural hypotension can occur, but is much less troublesome than with the agents discussed below. Side effects, which increase with dosage, are referable primarily to the central nervous system and to increased activity of the parasympathetic nervous system. Central nervous system side effects include nightmares, sedation, psychotic depression which may lead to suicide and Parkinsonism. Increased parasympathetic activity is expressed primarily as increased gastric secretion, which may induce or reactivate peptic ulcers, and increased gastrointestinal motility producing diarrhea. In general, the rauwolfia alkaloids are reasonably well tolerated in small doses, but these alone usually are inadequate to control the blood pressure of more severe hypertensives, and increased dosage is rarely justified.

Ganglionic blocking agents

These compounds act specifically to depress transmission through autonomic ganglia, and except for the secondary amines mentioned below, are among our most specific pharmacological agents[41]. All of the agents in common use can effect essentially complete blockade of sympathetic ganglia, and thus are among the most powerful hypotensive agents known. As would be expected, this high effectiveness produces a severe depression of compensatory reflexes, and postural hypotension is prominent. Only minor, clinically unimportant differences in the blockade of sympathetic and parasympathetic ganglia are found among this group of drugs, and consequently, parasympathetic activity and sympathetic vasoconstrictor tone are decreased in parallel. The most important complications of therapy with the ganglionic blocking agents result from decreased parasympathetic activity. These include constipation and even complete adynamic ileus, urinary retention, impotence, dry mouth and cycloplegia.

Most of the currently available ganglionic blocking agents are quaternary ammonium compounds, and therefore are very poorly absorbed after oral administration. They usually can be given in sufficiently large doses to produce the desired effects, but this leads to an unstable situation in which the gastrointestinal tract always contains an overdosage of the drug. A relatively small margin of overtreatment may cause constipation, which in turn decreases elimination of the excess drug and further increases the overdosage. This cycle must be carefully watched for and promptly treated. Certain secondary amine ganglionic blocking agents, mecamylamine (Inversine[R]) and pempidine (Pempiten[R]) are well absorbed, and in general, are easier to control than the quarternary agents. However, they are less specific in their actions on autonomic ganglion and side effects referable to the central nervous system and to the peripheral neuromuscular system can develop[2].

Inhibition of adrenergic mediator release

Drugs acting by this mechanism have only recently been described, and the only agent of this type available for clinical use is bretylium (Darenthin[R])[5]. In common with the adrenergic blocking agents, this material can effectively inhibit adrenergic vasoconstriction without altering parasympathetic nervous system function. Because

it inhibits the release of adrenergic mediator at all sympathetic nerve endings, reflex tachycardia is minimal. Preliminary reports on the use of bretylium in the treatment of hypertension are promising, but its potentialities cannot yet be fully evaluated.

Adrenergic blocking agents

Many types of compounds fall into this classification and all have in common the property of blocking excitatory responses of smooth muscle and gland cells to adrenergic stimuli, but of failing to block inhibitory responses (relaxation of bronchi, etc.) or adrenergic cardiac stimulation. By far the most important of the excitatory responses inhibited by these agents is the vasoconstriction induced by noradrenaline released at sympathetic nerve endings. The only drug in this category employed clinically as a hypotensive agent is phenoxybenzamine (Dibenzyline^{R}), but the characteristics of its blocking action are very similar to those of many other closely related compounds which have been studied pharmacologically[36, 38].

Dibenzyline^{R} can block sympathetic vasoconstriction as completely as can the ganglionic blocking agents, and the tendency to produce postural hypotension is similar. However, because it does not block adrenergic stimulation of the heart, reflex tachycardia in response to the fall in blood pressure is more prominent after Dibenzyline administration. This tachycardia represents the major disadvantage of this agent in the treatment of hypertension, and partially successful attempts to control the tachycardia have been made by combining Dibenzyline^{R} with agents inducing a bradycardia, particularly the rauwolfia alkaloids[14]. In contrast to the ganglionic blocking agents, the adrenergic blocking agents do not inhibit responses to parasympathetic nervous system activity, and consequently, the latter do not produce the many side effects associated with inhibition of parasympathetic function.

Summary

It is unlikely that a really rational therapy for essential hypertension will be developed until more information regarding the etiology of the disease is available. At the present time, one of the major approaches to the treatment of this condition is by means of surgical procedures or drugs which decrease sympathetic (adrenergic) vasoconstrictor tone. It is quite clear that derangement of sympathetic nervous system function is not a major factor in human essential hypertension. Consequently, treatment with any of these agents must be considered to be symptomatic only. By definition, lowering the blood pressure is treatment for hypertension, but it is not necessarily treatment for hypertensive cardiovascular disease. This fact must constantly be kept in mind as it has an important bearing on the selection of cases to be treated and the extent to which side effects and complications of treatment are tolerable.

Simple manometric success in lowering the blood pressure clearly is beneficial to patients with malignant or premalignant hypertension, but similar benefits to the much more common cases of "benign" essential hypertension is far from established. All drugs which inhibit sympathetic vasoconstrictor tone show appreciable toxicity and side effects, some more than others, and these undesirable effects must be carefully balanced against the benefits to the patients. The many new hypotensive drugs which have become available during the past decade have provided the physician with a powerful array of weapons with which to control the blood pressure. However, they also have made hypertension one of the easiest diseases to overtreat, not in terms of excessive lowering of the blood pressure, but in an imbalance between the expense, inconvenience, discomfort and physical danger of the therapy and its possible beneficial effects.

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The Abnormal Electrocardiogram Without Other Manifestations of Heart Disease

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With the emphasis on preventative medicine and early diagnosis, increasing use is being made of the electrocardiogram as a method of detecting subclinical heart disease particularly coronary artery disease. Today the medical assessment of a middle aged executive which does not include this test would be considered by many to be incomplete. It is often ordered routinely before surgical operations and electroshock therapy, and is one of the requirements when applying for large amounts of life insurance. The fact that the electrocardiogram is relatively easy to record and provides a permanent objective record for future reference makes it a particularly attractive adjunct to periodic health examinations whether they be carried out in private practice, industry or the armed forces.

The natural history of coronary artery disease has been well documented beginning with its first clinical manifestation but less is known about changes in structure and function that occur before signs and symptoms appear. How long they may be present, what factors control their rate and pattern of progression and whether or not they are reversible during the subclinical phase is not clearly understood. Confidence in the electrocardiogram as a diagnostic aid is based largely upon clinical trial supported by abundant physiological and pathological evidence. Whether an abnormal electrocardiogram recorded on a "healthy" person necessarily has the same clinical connotation as it has in the presence of manifest disease is problematical and certainly its place in forecasting future clinical events has yet to be evaluated. This can probably be said also about deviations in other biophysical or biochemical measurements recorded on apparently healthy people. For example, a characteristic glucose tolerance curve confirms the diagnosis of diabetes mellitus in a patient exhibiting signs and symptoms of the disease, and the height of the curve may give some indication of its severity. The apparently healthy offspring of a diabetic parent, on the other hand, may demonstrate a similar defect in his ability to metabolize glucose, but from this it is not possible with any degree of accuracy to predict when he will, if ever, develop other evidences of the disease; nor will it foretell the probable severity of the disease, should it appear. It is important therefore to recognize these limitations when applying tests of this type to asymptomatic individuals. The interpretation the physician places on an abnormal electrocardiogram discovered under these circumstances may have far reaching effects upon the individual, not the least of which may be the production of iatrogenic disease. The uncritical evaluation of the electrocardiogram may also have such practical implications as the loss of a flying license by a commercial pilot with consequent economic disaster, or result

in an application for life insurance being rated or declined.

To investigate this problem a long term follow-up study was undertaken in the Department of Medicine of the University of Manitoba on a group of healthy Royal Canadian Air Force and commercial pilots who had routine electrocardiograms taken during World War II. By 1948 contact was established with 3983 suitable persons who were in good health when their original electrocardiograms were recorded. Since then these people have submitted to re-examinations and electrocardiograms at intervals of five years. The mean age of the population when the study began was 27 years and at the present time it is approximately 40 years. With the passage of time, two groups are beginning to emerge. One consists of people who, while still in good health, have shown fixed or transient changes in their electrocardiograms and the other, of people who have developed some clinical form of heart disease and this, with three exceptions, has meant coronary heart disease. It is anticipated that from now on heart disease in this population will be restricted, with few exceptions, to coronary artery disease, changes secondary to hypertension and to other degenerative processes. The collection of data must continue until the size of these special groups is large enough to permit positive identification of those electrocardiographic variants, recorded in series, that mark the presence of progressive subclinical disease. As there is no reason to suspect that these states will develop prematurely in this highly selected group of people, it will be necessary to wait until they reach the age at which such changes are commonly observed.

This longitudinal survey, apart from any contribution it may make to the understanding of abnormal electrocardiograms in apparently healthy people, offers a unique opportunity to observe other factors in a maturing population; particularly will it assist in documenting the natural history of hypertension and obesity and as a further biproduct should provide accurate data on the incidence and prognosis of acute myocardial infarction.

The day to day technique of maintaining contact with approximately 4000 widely dispersed individuals may be of interest. At the beginning of each year, contact postcards are mailed to all participants. If these are not returned promptly tracing action is taken which involves reference to city directories, telephone books, places of employment and next door neighbors. Arrangements have also to be made for the examination of those whose five year anniversaries fall due during the year. In the majority of cases this presents no difficulty. In some it takes months and even years to get them to the doctor. To accumulate reliable data on the cardiovascular health of this population it is also necessary to obtain full details of all cardiovascular illnesses including copies of electrocardiograms and hospital and office records. A full description of terminal illnesses and postmortem examinations is essential.

The first general analysis of the accumulated data was undertaken in 1958, approximately ten years after the population was sealed. Pertinent information on each subject was transposed on to IBM punch cards. This included in addition to identification, age and past history of rheumatic and scarlet fever, the presence of obesity, hypertension, electrocardiographic abnormalities and all instances of clinical heart disease. After the necessary tabulations were completed, the original and a duplicate set of cards were stored for future reference in different locations as a precautionary measure against fire. General analyses of this type are time consuming and will be repeated only at infrequent intervals. The results of the 1958 review are to be published in detail[1]. While it is too soon to reach any final conclusions, experience to date with some of the larger classes of specific electrocardiographic variants is of general interest as it forecasts the type of information that is possible to develop through longitudinal studies of this type.

Partial Heart Block

There are 76 subjects who on at least one occasion have shown partial heart block. The age of these people when the abnormality was first observed varied from 18 to 61 years, the mean age being 29.6 years. Since then they have been followed for an average of 11.6 years. The past history of scarlet and rheumatic fever in this group was no greater than for the total population. Only one has dedeveloped coronary heart disease and there is nothing to suggest that these factors were causally related. There have been three deaths, each due to accident. A preliminary report[2] in 1952 on 57 of these people pointed out that in serial records partial heart block was a variable function in 89 percent of cases and remained fixed in only 11 percent. There has been one example of partial heart block progressing through to complete block but this subject still shows no clinical manifestations of disease.

Wolf Parkinson White Syndrome

The electrocardiograms of 13 subjects have shown the classical Wolf Parkinson White configuration. This variation was first observed at a mean age of 28.2 years and has been followed for an average of 8.0 years. There have been no deaths and none has shown clinical evidence of heart disease apart from four who have had episodes of paroxysmal tachycardia.

Right Bundle Branch Block

Right bundle branch block was observed in the electrocardiograms of 30 individuals at a mean age of 28.1 years. Since the appearance of this abnormality, the group has been followed for an average of 10.0 years. There have been two deaths, both due to accident, and none so far has developed clinical evidence of myocardial disease. In four

instances right bundle branch block appeared after entry in the study.

What will happen to the health of the people in these three groups as they grow older is not known. Certainly at the observed ages partial heart block, the Wolf Parkinson White configuration and right bundle branch block have not been forerunners of manifest heart disease.

High QRS Voltage

High QRS voltages were observed in nine subjects whose mean age on entry was 34.5 years and the abnormality was first recorded at a mean age of 42.3 years. In each instance the increased voltages were associated with RS-T and T wave changes. They have been followed for an average of only 4.0 years since the abnormality was noted. Seven of these people have hypertension. In one, following sympathectomy the hypertension disappeared and the electrocardiogram returned to normal. Three have developed acute myocardial infarction. There have been no deaths.

Primary T wave Changes

The electrocardiograms of 114 subjects have shown primary T wave changes on at least one occasion. This includes both deviations of the T wave vector to the right and to the left as seen in the frontal plane, as well as low voltage T waves and segmental changes that were apparently not reciprocal. The variants appeared at a mean age of 33.7 years and have been followed for 7.3 years. A fixed or transient elevation of the blood pressure was recorded in 26 of these people. Seven have developed coronary artery disease and there have been four deaths, two of which were due to myocardial infarction and two to accidents. In those developing myocardial disease the T wave changes occurred at a mean age of 46.4 years to be followed 3.6 years later by the clinical event. In some instances it was possible to confirm, either by the location of the pathological Q waves at the time of infarction or from postmortem examination of the heart, that the T wave variations accurately identified the area of myocardium which was about to infarct.

Primary T wave changes may be due to a variety of causes including pericarditis, intercurrent infections, the postprandial response, the position of the patient, serum electrolyte changes, myxoedema, gall stone colic as well as other aetological factors yet to be identified. There is little doubt that in some instances it is due to myocardial ischemia. T wave variations of this type, whether fixed or intermittent, when present in the serial tracings of a person over age 40 should raise the suspicion of coronary insufficiency. They were observed intermittently in the serial electrocardiograms of one of our cases for six years before infarction occurred in the area of myocardium under suspicion.

While in selected cases there is good evidence that specific changes in the electrocardiograms of asymptomatic people were related to the clinical events which followed, it is important to emphasize that there are many subjects showing these and other variations in their electrocardiograms who after many years, are apparently in good health and free from other evidence of heart disease.

At the time of the 1958 analysis, 32 subjects had developed clinical evidence of myocardial disease. In 17 of these the serial electrocardiograms were completely normal prior to the clinical event and in 15 they identified accurately the presence of progressive subclinical myocardial disease. Since that time a further eight cases have been noted. In three of these the routine electrocardiograms accurately predicted the events which followed while in the other five they were not diagnostic.

Summary

In summary it was pointed out that electrocardiographic concepts validated empirically on patients with known heart disease should be used with caution when interpreting the abnormal electrocardiogram of an apparently healthy person. A brief description has been given of a long term electrocardiographic follow-up study designed to throw light on the course of subclinical heart disease and thereby help to establish with more accuracy the significance of specific changes in the electrocardiograms found under these circumstances. The results of the survey to date have been highlighted. Certain specific electrocardiographic abnormalities have not so far been forerunners of recognizable heart disease while others appear in some instances to be clearly related to it. It was emphasized that electrocardiographic changes which are of diagnostic significance in the usual clinical sense, may be present in the electrocardiograms of apparently healthy people for many years.

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Congenital Heart Disease: Incidence of Lesions, Familial Factors, Course and Complications in 666 Patients

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Since 1953, 666 patients with congenital heart disease have been referred for investigation to the Cardiopulmonary unit of the University of Alberta hospital. Clinical diagnoses have been established by physical examination, electrocardiographic and radiologic studies. In 463 instances confirmation has been obtained by cardiac catheterization, in some instances supplemented by angiocardiography. Of the remaining 203 patients, those with uncomplicated patent ductus arteriosus or coarctation of the aorta had the diagnosis confirmed at operation. Diagnoses of aortic stenosis were usually made on clinical grounds as will be outlined later, and confirmation of the diagnoses in the remainder was obtained at autopsy.

Data concerning the incidence of various lesions, comments concerning familial factors, the diagnosis, course and prognosis of these patients will, we hope, provide points of interest both for the referring physician and for workers in other cardiac investigation units.

The incidence of each of the major congenital heart lesions encountered in this group of patients is given in Table I. Some patients had more than one lesion.

Table 1
Incidence of Various Types of Lesions in 666 Patients with Congenital Heart Disease

Lesion	U.A.H. Number of pts.	U.A.H. % total	Wood (1) % total	Keith et al (2) % total
A.S.D. (Secundum)	99	15	18	7
V.S.D. (excl. tetrad)	150	22.5	11	25
P.D.A.	116	17.5	13	17
Pulm. Sten. alone	56	8.5	12	7
+ V.S.D.	75	11.25	11	11
+ A.S.D.	16	2.5	2	
Ao Sten or Ao. Atresia	48	7.25	3	6
Coarct.	22	3.3	9	6
Transposition Great Vessels	26	4	1	8
A.V. Canal or sept. prim.	27	4		2
Tricuspid Atresia	12	2	1.5	3
Miscellaneous	29	4.5	3.7	

Familial, Perinatal and Related Factors:

Of the 666 patients, 16 (2.5%) had siblings with congenital heart disease and in a further 29 instances other members of the immediate family had congenital heart disease. Thus, of our patients, a history of congenital heart disease in close relatives was obtained in 6.8%. This is in contrast to "2 per 100 families" reported by Polani and Campbell[3] and an incidence of 0.60% reported by Kjellberg[4]. Other associated congenital lesions (excluding Mongolism) were present in 66 (10%) of our patients. Only 7 (1%) of our patients were Mongols. Other congenital lesions (non-cardiac) were present in the siblings of 18 (2.7%) of the group, a figure corresponding closely to the number of patients having siblings with congenital heart disease.

Birth weights were recorded as a routine and it was found that 90.5% of the total number of patients weighed 5 pounds or more at birth. Although we have not attempted to compare these results with those from the general population we doubt that the number weighing less than 5 pounds at birth is significant.

Complications and Mortality:

The data presented in Table 2 require little comment.

Table 2
Incidence of Complications

Complication	% of Total	Comment
Heart Failure		
Total	14%	
Cyanotic	7%	28% of cyanotic patients
Acyanotic	7%	9.4% of acyanotic patients
Syncope or Convulsions		
Total	27% *	
Cyanotic	11.4%	34% of cyanotic patients
Acyanotic	15.6%	23% of acyanotic patients
Cerebral Thrombosis	0.3%	2 patients — both cyanotic
Bacterial Endocarditis	1%	1 cyanotic patient 6 acyanotic patients

*This group comprises 219 patients from whom this information was sought.

The observation that heart failure was three times more frequent in cyanotic than in the acyanotic patients probably reflects both the more serious nature of many of the lesions producing cyanosis and readier recognition of right-sided than left-sided failure. Those patients who were classed as having syncope usually had a history of several episodes of unconsciousness; we accepted for this classification a single convulsive seizure including any occurring during febrile childhood illness. These data are presented as observations and no analysis of either cause or significance will be attempted.

Frequent respiratory infections were encountered in some patients, particularly those with shunts

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leading to increased pulmonary blood flow. Precise figures as to the incidence of this complication are not, however, available from our data.

The overall mortality, including operative and post-operative deaths, was 17.6% during the six year period of observation. A contrast becomes apparent, however, when the cyanotic and acyanotic patients are considered separately. In the group of cyanotic patients the mortality was 44.3% whereas in the acyanotic group the mortality was only 8.6%.

Two hundred and eleven patients were subjected to operation; 127 operations included the use of extracorporeal circulation. The indications for operation in these 211 patients were those generally accepted for each particular lesion and this proportion (31.7%) of the total provides some indication of the number requiring operation in a group of referred patients with congenital heart disease.

Physical Examination:

Some physical findings such as cyanosis and finger clubbing are well recognized indications for further and detailed investigation. Other points in the physical examination which we believe are very helpful in assessing the type and severity of congenital cardiac lesions will briefly be mentioned. Recognition of these findings has proved of value to us in indicating both the desirability and possibility of surgical help and in assessing the degree of urgency with which surgery should be considered.

Evidence for ventricular hypertrophy should always be sought on palpation of the precordium. The well localized thrusting apex beat of left ventricular hypertrophy—perhaps displaced to the left—provides valuable evidence for a diagnoses of aortic stenosis for instance. Such evidence for left ventricular hypertrophy can be considered an indication for left ventricular pressure measurements. In our own experience such a localized thrusting impulse has provided evidence for left ventricular hypertrophy which has proved at least as reliable as that adduced from electrocardiographic and radiologic studies.

Right ventricular hypertrophy can be recognized by the presence of a diffuse heaving impulse felt over the whole precordium internal to the apex, often extending over the outflow tract of the right ventricle. This is always an abnormal finding although care must be taken in interpreting this sign in children and adults of thin build with thin chest walls. Once recognized, the cause of right ventricular hypertrophy is usually evident when either the typical systolic thrill and ejection murmur of pulmonary stenosis or the palpable basal second sound of pulmonary hypertension is sought. For completeness, the physical findings attributable to pulmonary hypertension are illustrated in Figure 1.

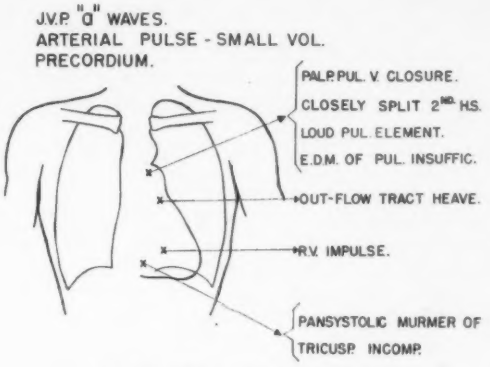

Figure 1

The greatest degrees of activity of the right ventricle in our experience have been associated with atrial septal defects. Such activity together with absence of a normal left ventricular impulse and the presence of a widely split basal second sound—the duration of splitting being unchanged during the varying phases of respiration—makes this diagnosis as certain clinically as any in the field of cardiology.

Finally, a word about the diagnosis of aortic stenosis in children. In its fully developed form, evidence for hypertrophy of the left ventricle together with the basal systolic ejection thrill and murmur, conducted into the arteries of the neck and sometimes down to the apex, make the diagnosis a relatively simple one. Lesser degrees of obstruction at the aortic valve, however, give rise to less obvious signs and evidence for left ventricular hypertrophy may be lacking. Differentiation of mild degrees of aortic stenosis on the one hand from ejection murmurs arising in the left ventricular outflow tract on the other hand can be difficult. A point which we regard as of value in separating these two causes is the presence or absence of a systolic ejection click. Such a sound following closely after the first heart sound and initiating the ejection murmur signifies some degree of dilatation of the aortic root. Such dilatation is frequently associated with aortic stenosis and well merits the term "post-stenotic dilatation" so frequently applied to it.

Referral for Investigation:

Where the diagnosis is clinically obvious, as for example, patent ductus arteriosus or coarctation of the aorta, special investigation is rarely required and surgery can be undertaken electively. Nevertheless, it should be remembered that these lesions may be associated with other and less easily recognized lesions, and if complications of this sort are suspected because of any atypical features in the case fuller investigation is merited.

Any cyanosed child should be investigated fully because the lesions causing cyanosis are frequently more serious and often unexpectedly complex. Full information is desirable before surgery is undertaken. Cardiac catheterization and angiocardiography can, if necessary, be carried out within weeks or even days of birth.

Recognition of pulmonary stenosis is important, especially if it is associated with other lesions such as a ventricular or atrial septal defect. This is because pulmonary stenosis is usually associated with a relatively normal pulmonary vascular bed, and thus the complex lesions of which pulmonary stenosis is a part are frequently amenable to full surgical correction with excellent results.

Pulmonary hypertension should be recognized because it is a consequence of vascular changes in the small pulmonary arteries and arterioles. These changes may in time become irreversible and preclude satisfactory results from even perfect intracardiac surgical repair. Provided blood is still being shunted in appreciable amounts from the left to the right side of the heart through a defect, closure of such a defect will reduce pulmonary blood flow and so reduce pulmonary arterial pressure to a point at which further damage to the pulmonary vessels becomes less likely. Indeed, regression of changes can be inferred from the results of follow-up studies of pulmonary vascular resistance in some of our patients after cardiac operations. Many problems remain to be resolved in the treatment of this particular group of patients with the unhappy combination of small left to right shunts and associated pulmonary hypertension.

Summary:

A study of incidence of lesions, familial factors, diagnosis and course in a group of 666 patients with congenital heart disease has been presented.

The lesions diagnosed most frequently were ventricular septal defect, pulmonary stenosis alone and combined with other lesions, patent ductus arteriosus and atrial septal defect.

A history of congenital heart disease in siblings or members of the immediate family was obtained in 45 instances.

The mortality of the group with cyanosis was 44.3% in contrast to 8.6% in the group classed as acyanotic.

Operations were performed on 31.7% of the total number. We believe that careful physical examination provides much information concerning the nature of the lesion, the desirability of referral and the possibility of corrective surgery.

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Phonocardiography in Clinical Cardiology

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The recording of heart sounds and murmurs is by no means a new technique. There has, however, been relatively little interest in phonocardiography until recent years. The reason for this has been due largely to our misunderstanding of how the technique should be used. The phonocardiogram cannot replace the stethoscope in auscultation of the heart, and, in fact, is not as good as the intelligent use of the clinical stethoscope in the actual appreciation of heart murmurs. Frequently the phonocardiogram fails to record murmurs that can be heard with the stethoscope, while on the other hand it may record vibrations that cannot be heard, depending on the type of instrument and frequency response of the system used. Phonocardiography cannot be used in clinical cardiology in the same manner as electrocardiography. It is, however, of considerable help in the analysis of many diagnostic problems and should be used, as far as diagnosis is concerned, in selected cases where some problem exists with regard to the significance of added sounds or murmurs heard on clinical auscultation. Phonocardiography at the present time, with present non standardized equipment, would be of little or no value as a routine procedure. This is largely due to the considerable number of unavoidable variables in recording sounds from the chest wall. Consequently, we should not expect the phonocardiogram to provide specific diagnostic patterns to nearly the same degree that can be expected from electrocardiography.

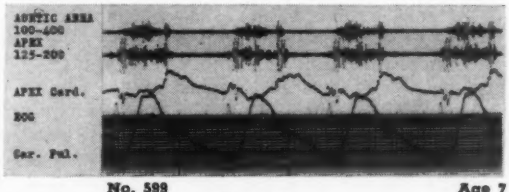
No general agreement has been reached as to standardization of phonocardiography. One can readily understand why this has occurred, when we consider the many different opinions as to whether we should attempt to record what we hear with the stethoscope or what actually occurs at the chest wall or whether we should select and amplify certain sound frequencies. A great deal of study has been carried out during the past 10 - 15 years on recording techniques, and a number of models

Supported by the Ontario Heart Foundation.

are now available commercially, many of which are quite adequate for practically all types of phonocardiographic study. One, however, has to possess a dedicated interest in phonocardiography, if he is to gain useful diagnostic information from this technique. We have adopted a somewhat unique approach, and for some years have applied the principle of selective phonocardiography, utilizing a multi-channel cathode ray technique with a direct recording variable speed camera (Figure 1). In this manner two or more areas (for example mitral and aortic) can be recorded simultaneously,

Figure 1
Multi-channel cathode ray phonocardiographic apparatus.

using a selected frequency range (by means of Khronhite band pass filters) together with carotid pulse, respirations, the electrocardiogram, apex cardiogram and venous pulse. Such a technique allows direct continuous monitoring of the heart sounds, murmurs, and other parameters in studying the case, a recording being made at any desired time during the study (Figure 2).



No. 599 Age 7

Figure 2
Phonocardiogram in a case of congenital aortic stenosis. From above down aortic area (100-400 cycles), mitral area (125-200) apex cardiogram, E.C.G. carotid pulse.

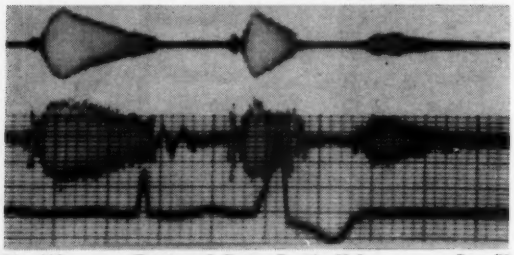
There are three applications of phonocardiography in clinical cardiology, namely diagnosis, teaching and clinical research. Since in this short review we are primarily concerned with the diagnostic applications of phonocardiography, its use in other fields will not be discussed except to comment briefly on clinical teaching. By means of multiple electronic stethoscopes large groups of students can see and hear the sounds and murmurs of any particular case being presented. To do this, a large cathode ray tube (Figure 3) with a long persistance screen

Figure 3
Apparatus used in clinical teaching. (Tape Library in background)

and slow sweep speed is used. In this manner the phonocardiogram is both visualized and heard at the same time. In addition to the case being presented, a number of similar cases previously recorded on tape can also be reproduced for visual and acoustic study. We have recorded over 600 cases on tape, and continue to make tape recordings of practically all cases when the phonocardiogram is done. This provides a very useful library for teaching, and for comparison with later follow-up studies. The use of suitable amplifying and filtering techniques and the stethophones rather than a loud speaker makes it possible to reproduce heart sounds and murmurs exactly as they are heard by the physician with his stethoscope.

With regard to the use of phonocardiography in clinical cardiology some might question its value compared to the intelligent use of the simple

stethoscope. It must be emphasized that phonocardiography is not a substitute for the stethoscope, but merely an aid in confirming our findings on auscultation, and in timing of sounds and murmurs in relation to the cardiac cycle. In this regard it is, however, of considerable value particularly if we can by frequency selection isolate, record and study the various sound phenomena produced during the cardiac cycle. Furthermore, by the continued use of phonocardiography one learns and more readily understands and appreciates the significance of what is heard on clinical auscultation. All of us are familiar with the problems of auscultation—not whether a murmur or added sound is present or not, but the timing of the adventitious sound and its exact relation to the haemodynamic events of the cardiac cycle. We have all been confronted with the problem of whether a murmur is in early, mid or late systole, whether or not a systolic or diastolic gallop is present, whether the second heart sound is abnormally split, whether the sound heard is an opening snap, and even, on occasion, as to whether a murmur is systolic or diastolic (Figure 4). Phonocardiography can be of



No. 262 Ruptured Cusp. Aortic Valve Age 76

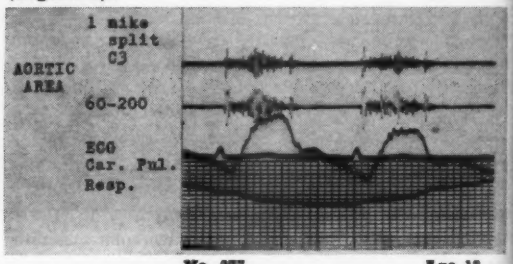
Figure 4

Musical diastolic murmur aortic area. Clinically this was considered to be a systolic murmur.

considerable help in many of these cases, and, in addition, has increased our knowledge considerably as to the significance of added sounds such as the systolic ejection click, the delayed pulmonary closure, the opening snap, the third heart sound. It has clarified the diagnostic significance of the ejection as compared to regurgitant systolic murmurs and has aided greatly in our appreciation and understanding of these sounds and murmurs in clinical auscultation.

In this review an attempt will be made to illustrate briefly our approach by means of selective phonocardiography to the study of heart sounds and murmurs, and at the same time indicate the possible role of phonocardiography in clinical cardiology.

Although it is not possible to cover all of the many problems encountered in auscultation of the heart in this review, a number of examples in which the phonocardiogram has been of considerable help will be discussed. Most important of all is a clear understanding of the fundamental haemodynamic events of the cardiac cycle (Figure 5), which is essential, if the observer is to interpret the significance of variations in heart sounds and the production of murmurs when pathological or physiological alterations occur. Broadly speaking, heart sounds and murmurs are produced by the haemodynamic events occurring during the cardiac cycle. The first heart sound is produced essentially by closure of the tricuspid and mitral valves. Systole is normally silent. If, however, obstruction is present at the aortic valve, the streamline flow is disturbed and turbulence beyond the obstruction results in a noise or murmur. Considering again the cardiac cycle this murmur will be loud, harsh, and blowing in character due to the high pressure behind it, and the rapid forceful ejection of blood from the left ventricle. Furthermore, the murmur will begin slightly after the first heart sound since, as we know, the first heart sound occurs at the beginning of ventricular systole (isometric contraction) however, the aortic valve cannot open until pressure within the left ventricle has exceeded that in the aorta (diastolic pressure). There will therefore be a slight delay following the first heart sound before the murmur of aortic stenosis begins, and also this murmur will grow in intensity corresponding to the maximum flow over the stenosed valve and diminish as flow decreases toward the end of systole. The haemodynamic events associated with an obstructed left ventricular outlet thus result in the typical "ejection" murmur which presents specific features in the phonocardiogram (Figure 6).



No. 377 Age 18

Figure 6

Aortic stenosis, classical murmur with characteristics related to specific events of cardiac cycle (see text).

An excellent example of how alterations in haemodynamics explain the findings on auscultation is found in congenital atrial septal defect. Here the phonocardiogram in conjunction with the fluoroscopic, electrocardiographic and clinical findings is of considerable value. Let us consider for a moment the cardiac cycle in A.S.D. where the right atrium receives not only the venous return from the vena cavae but also a considerable volume of blood from the left atrium. The increased volume flow over a normal pulmonary valve will produce a systolic murmur, as the large volume of blood is rapidly ejected from the right ventricle. Because of the increased filling of the right ventricle, it takes longer to empty and this results in a delayed

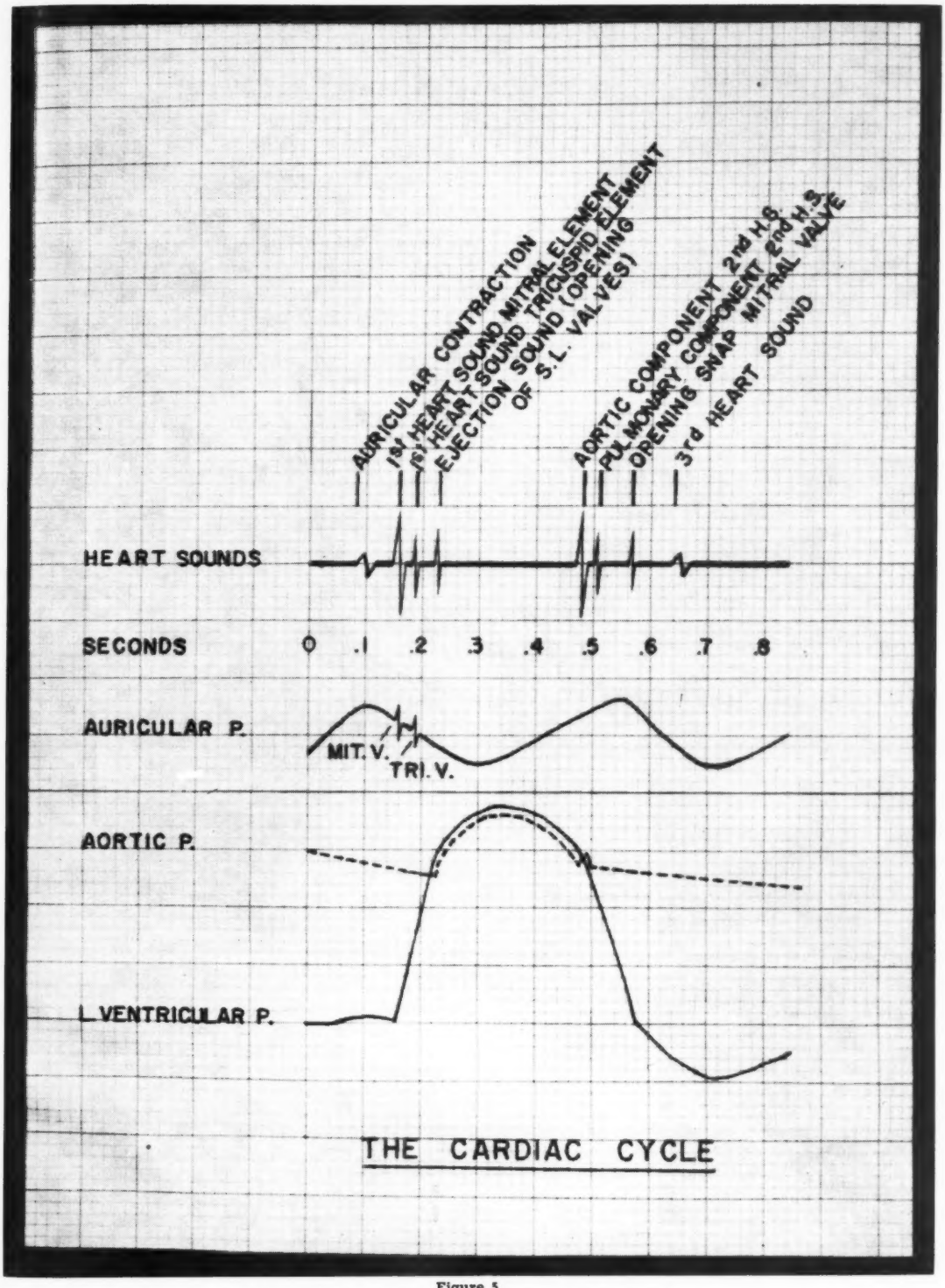


Figure 5
Diagram of sound events during a normal cardiac cycle.

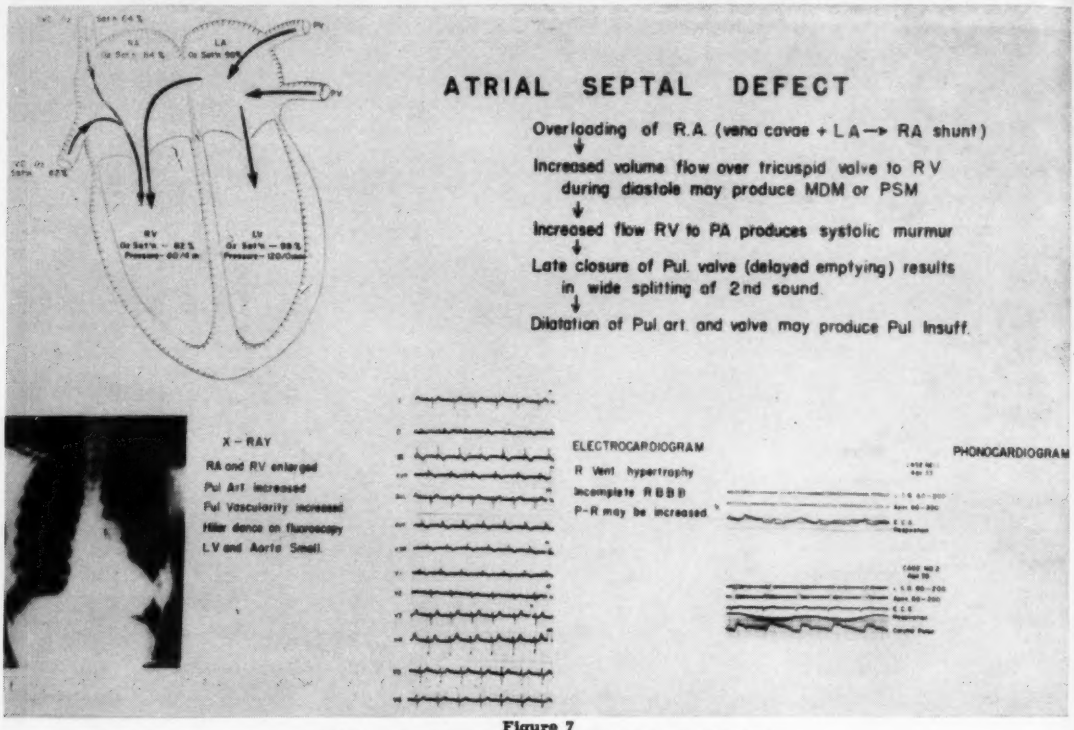
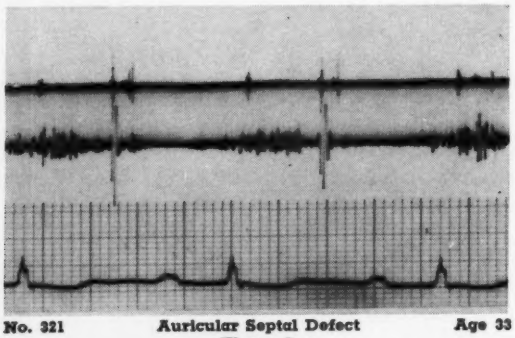

ATRIAL SEPTAL DEFECT
Overloading of R.A. (vena cavae + L A → RA shunt)
Increased volume flow over tricuspid valve to R V during diastole may produce MDM or PSM
Increased flow RV to PA produces systolic murmur
Late closure of Pul. valve (delayed emptying) results in wide splitting of 2nd sound
Dilatation of Pul art. and valve may produce Pul. Insuff.
X – RAY
RA and RV enlarged
Pul Art increased
Pul Vascularity increased
Hilar dance on fluoroscopy
L V and Aorta Small
ELECTROCARDIOGRAM
R Vent. hypertrophy
Incomplete R B B B
P-R may be increased
PHONOCARDIOGRAM

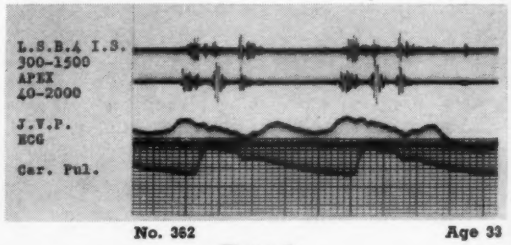
Figure 7
Clinical and laboratory features in atrial septal defect



No. 321 **Auricular Septal Defect** **Age 33**

Figure 8
Phonocardiogram in advanced atrial septal defect. (This case was considered and treated as rheumatic mitral disease prior to investigation). Note wide splitting of second heart sound, systolic and diastolic murmurs. Wide splitting of second heart sound was interpreted as opening snap and mid-diastolic murmur of mitral stenosis.

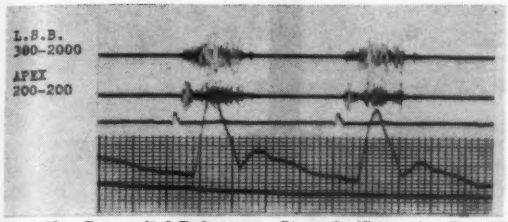
closure of the pulmonary valve, producing a wide splitting of the second heart sound. The increased volume flow leads to dilatation of the pulmonary artery and outflow tract, and eventually to a degree of pulmonary insufficiency producing an early diastolic murmur. Furthermore, the torrential flow over a normal tricuspid valve may also produce a rumbling mid-diastolic murmur (Figure 7). When this happens some confusion with rheumatic mitral stenosis occurs, and we have recently demonstrated a diagnosis of A.S.D. by cardiac catheterization in



No. 362 **Age 33**

Figure 9
Short early diastolic murmur of pulmonary insufficiency in a case of A.S.D. Note aortic closure and diastolic murmur following pulmonary second sound.

two cases referred initially to us as rheumatic mitral disease for investigation prior to surgical treatment (Figure 8). At times the phonocardiogram can be of help in differentiating between the early diastolic murmur of aortic and pulmonary incompetence, if by frequency selection we can demonstrate a clear splitting of the second heart sound with the murmur following the pulmonary element (Figure 9). It has been shown that there is a definite relationship between the duration of splitting of the second heart sound and the degree of pulmonary stenosis — the greater the split the more severe the stenosis. The phonocardiogram is essential to demonstrate the duration of the split. We frequently are unable to hear the faint pulmonary closure in cases of pulmonary stenosis, which

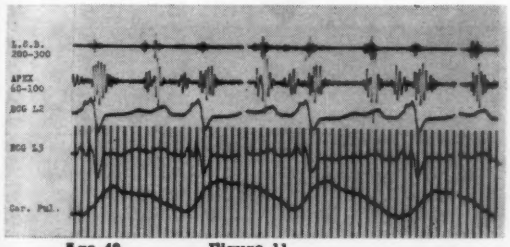


No. 482 Congenital Pulmonary Stenosis (Severe) Age 17

Figure 10

Pulmonary stenosis. Classical ejection murmur with marked delay of pulmonary closure not heard on clinical auscultation.

is often recorded in the phonocardiogram (Figure 10). Again the phonocardiogram is of value in demonstrating the type of gallop or triple rhythm present. In a recent case of unknown etiology it was felt, on auscultation, that the patient presented a mid or late systolic click whereas the added sound was shown by the phonocardiogram to be a late diastolic (pre-systolic) triple rhythm or gallop, and therefore of much more clinical significance than concluded from auscultation (Figure 11).



Age 40 Figure 11

Cardiomegaly and congestive failure. Clinically interpreted as mid or late systolic click. Note diastolic triple rhythm or gallop.

Although a third heart sound is associated with mitral insufficiency, and an opening snap with mitral stenosis, occasionally both occur in the same case. When this is suspected, on auscultation, the phonocardiogram is usually of considerable help and often demonstrates considerably more than is suspected on auscultation (Figure 12).

Recently, very small microphones mounted at the tip of a number 5 (no lumen) or number 9 (with lumen) cardiac catheter have been developed. These crystal type microphones are very fragile and expensive at the present time. Although our experience with intracardiac phonocardiography is so far quite small, it is apparent that this method is a most useful one in localizing heart murmurs within the heart during cardiac catheterization. The microphone tip records a murmur at its origin, and consequently in a case of pulmonary stenosis a good recording of the murmur at and just distal to the pulmonary valve will be obtained. When the catheter tip (microphone) is withdrawn into the right ventricle the murmur disappears. In systolic murmurs due to aortic or mitral lesions no murmur is recorded during a right sided catheter study,

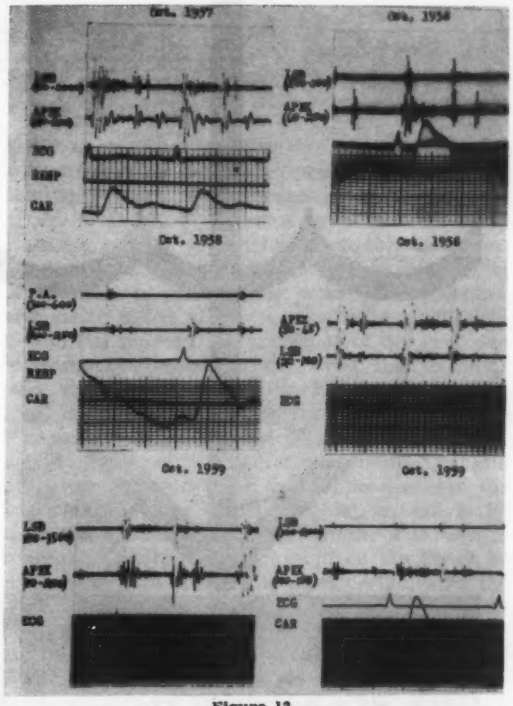


Figure 12

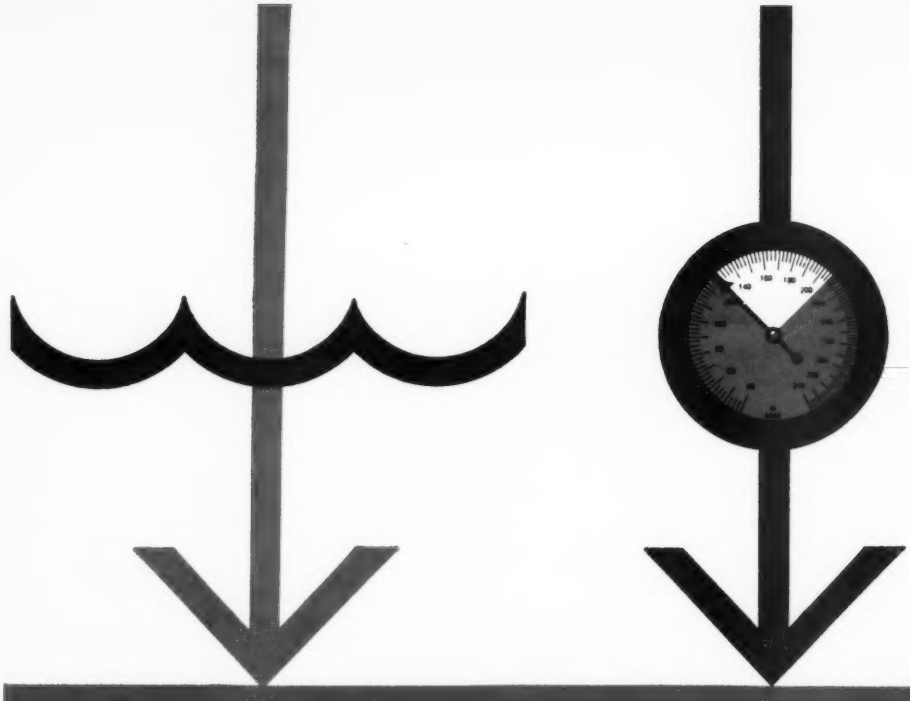
Serial phonocardiography in a very early case of rheumatic heart disease. In October, 1957, a systolic murmur and third heart sound was present with no other findings to suggest rheumatic heart disease. The phonocardiogram revealed an opening snap in addition to the systolic murmur and third heart sound. Later tracings revealed the development of a mid-diastolic murmur, and by 1959 the fluoroscopic findings and murmurs had progressed to a degree in which a diagnosis of rheumatic mitral disease was apparent.

whereas a good systolic murmur is recorded externally from the chest wall. This method is therefore, we feel quite selective and should be of value in localizing cardiac murmurs. More study with this technique, however, is required, and, of course, the method can only be applied in selected cases in whom cardiac catheterization studies are indicated.

To conclude it is apparent that phonocardiography is a useful and valuable technique in clinical cardiology. It cannot however be used in the same manner as the electrocardiogram, where a technician can do the complete recording, sending the tracing on to the cardiologist for interpretation. We should use the phonocardiogram in much the same manner as we use the stethoscope. No set routine can apply to all cases. In many instances an experienced technician can record what the cardiologist requests, but ideally the cardiologist should personally supervise and carry out the examination, recording the various areas. and other parameters that he feels applicable to the particular case under investigation.

Acknowledgment

The apparatus used in this study was developed by Mr. Gordon Steward, who recorded the illustrations shown in this review.



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Editorial

S. Vaisrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

The National Heart Foundation of Canada

In an age abounding in "dedicated" weeks, "set aside" months, and "ear-marked" years — fire prevention week, brotherhood week, restaurant month, child dental health week, adolescent mental health week, geophysical year and many others, (the number is limited only by the narrow confines of the calendar)—the recent addition of a Heart Foundation month comes as no surprise. Nor is there much wonderment at the choice of February as the dedicated month, for is not February the month of St. Valentine — the patron Saint of the affairs of the heart? The surprise attaches itself only to the belatedness of the dedication to a matter so overwhelmingly important as the matter of the heart.

The Canadian Heart Foundation is a voluntary lay-medical association with aggressive intent toward heart disease. Its purpose is to combat cardiac crippledom and mortality by promoting research and education. To attain this end it engages in energetic fund raising endeavors and public enlightenment campaigns through the media of the lay press, radio and television — activities which reach their climax during the month of February, as well as in intelligent planning of the allotment of funds, which goes on quietly throughout the year. In both the "receiving" and the "giving" aspects of its function the Heart Foundation looks eagerly to the support, guidance and advice of the medical profession at large, to doctors out of as well as in the ranks of its membership, for it is not only the cardiologist who has an interest in heart disease. The surgeon, whose skill may be defeated by the patient's "cardiac status," the anaesthetist whose worried eye dare not leave for a moment his cardiac patient, the obstetrician apprehensive about the mother's cardiac reserve, the pediatrician baffled by a murmur, the general practitioner who treats heart cases every day — all have an important stake in heart disease. The heart is much too good an organ to be left to the cardiologist.

Indeed, it is much too good an organ to be left to any one specialty, or for that matter, to the exclusive concern of the practising clinician. The non-practising medical investigator, the para-medical biochemist and physiologist, the non-medical physicist, engineer, statistician, nutritionist — all have more than casual interest in the heart, to the study and understanding of which they have contributed so much.

It is with this universality of the subject in mind, that the Manitoba Medical Review ventured to dedicate an entire issue to the Heart Foundation, without fear of losing its "neutralist" status. In this issue there are gathered (through the good graces of Dr. R. E. Beamish) articles from many research centres in Canada, including our own. Hardly a comprehensive cross section, but rather a glimpse into some of the current investigation, and vistas of the future — these papers will convey to the reader the dimensions of the problems involved, the extent of the work that is being done, and the magnitude of the tasks that lie ahead. They denote by implication the importance of the National Heart Foundation.

If it can be safely assumed that the medical and allied professions will be fully appreciative of the importance of the Heart Foundation, can it be taken for granted that the lay public will react in a similar fashion? Will the man on the street be impressed? The answer is most certainly in the affirmative. The public is fully aware of the menace of heart disease. It is familiar through personal experiences as well as through media of mass communication with its mortality and morbidity. It is well acquainted with the epidemiologic aspects and the hypothetical etiologies of cardiac disorders. If anything, the public is overanxious, and will undoubtedly lend a willing ear and a helpful hand to the campaigners of the Heart Foundation.

There is yet another reason for the receptiveness of the public mind to the call of the Heart Foundation, a reason unrelated to the statistics of cardiac pathology. To the physician the heart may be nothing more than a glorified mechanical blood-propelling pump. To the layman (and the doctor off duty), however, the heart is not just an organ. It is "the" organ, the seat of affection, love, generosity — the symbolic essence of the inner self.

When Wordsworth refers to a "heart riven with vain endeavor," and Oliver Wendell Holmes to "hearts that break and give no sign," they obviously are not speaking of rupture of the myocardium. When Edith Sitwell states that "all great poetry is dipped in the dyes of the heart," she is not thinking of dye dilution techniques in the investigation of intracardiac shunts. Nor does Shakespeare's King Henry VIII allude to open heart surgery when he exclaims "I feel my heart new opened." These poets simply re-affirm the emotional and symbolic centrality of the heart in the mind of man. It is this non-organic connotation that assures a strong emotional response to anything that pertains to the heart.

Thus the layman, the clinician and the investigator have a stake in the National Heart Foundation

of Canada. They are all interested in its progress, and wish it well. In this they are joined by the Manitoba Medical Review, which is as proud of this dedicated issue, as it is grateful to all its contributors.

"Out of the fullness of the heart the mouth speaketh."

Ed.

♥

Obituary

Dr. Alvin T. Mathers

Dr. Alvin T. Mathers, 71, died in Deer Lodge Military Hospital on January 4th after a distinguished career in psychiatry and medical education. His father was editor of the first newspaper in Portage la Prairie and his uncle was a chief justice of Manitoba but, as a boy, he decided on medicine. Born in Neepawa, he was educated there and in the University of Manitoba graduating M.D.C.M. in 1913. He did post-graduate work in Boston, France, Switzerland, Germany and England. For three years he was superintendent of Winnipeg Municipal Hospitals. From 1917 to 1918 he was Captain, R.C.A.M.C. at Tuxedo Barracks, then was appointed provincial psychiatrist, a post which he held until 1942 when he resigned. In 1931 he was appointed Dean of the Faculty of Medicine, University of Manitoba and held office till 1949 but continued to serve as a teacher of neurology and psychiatry until 1954 when he was appointed Professor Emeritus.

He had many other honours: LL.D. Manitoba 1949, senior member Canadian Medical Association 1959, president Winnipeg Medical Association, vice-president Manitoba Medical Association, president of the Royal College of Physicians and Surgeons of Canada, president of the Medical Council of Canada, secretary and president of the Association of Canadian Medical Colleges.

As provincial psychiatrist his psychiatric advice was made available in court cases and on numerous occasions he acted as a friend of the court. He gave advice in the case of the notorious Strangler Nelson. He was loaned as an expert witness in psychiatry to courts in North Dakota, Saskatchewan, Ontario and British Columbia.

He is survived by a daughter, Mrs. George Sheldon, Dubuque, Iowa and a sister, Mrs. C. W. Atkin of Winnipeg.

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Social News

Reported by K. Borthwick-Leslie, M.D.

Memo from Dr. Macfarland with an excerpt from Dr. A. T. Karsgaard, 2 Pine View Road, Abbottabad, West Pakistan — quoted ad verbatim:

We came back here in September and have enough work to do in helping the people of this area. There are about 10 doctors for 400,000 people. We have had over 100 cataracts to do and a certain amount of general surgery. This week we've had a couple of cataracts, a hare-lip, skin grafting on a 3½-year-old who was burned 8 months ago and was allowed to heal with his thighs flexed onto his abdomen (out in a village), and today an amputation of a foot which was crushed several days ago up on the mountain side by a falling stone. If any of the doctors would like to have a trip to see this part of the world, we could probably line up a few cases in their specialties which would make an interesting break on such a journey.

☆

The Manitoba Clinic announces the establishment of a Department of Dermatology under the direction of Robert Allardyce Main, M.B., Ch.B. (St. Andrew's), M.R.C.P. (Edin). Welcome to Winnipeg, Dr. Main.

☆

Charles Neville Crowson, M.D., Ph.D., certified Pathologist, announces his succession to Dr. A. E. Rodin, as Director of Central Medical Laboratories Ltd., 507-8 Boyd Building. Practice restricted to Clinical Pathology.

☆

Dr. Jean McFarlane announces the opening of her office, 432 Medical Arts, as of March 10, 1960. Dr. McFarlane is well known, specializing in Obstetrics and Gynaecology. All the best, Jean.

☆

A rather belated welcome to Dr. Ian M. Grant, 204 Professional Bldg. With a bit of "reporterish digging" I find that officially the title is Ian M. Grant, M.B., Ch.B. (St. Andrew's), Fellowship in Surgery London and Edinburgh. Certification, Tropical Medicine and Hygiene. To my chagrin, find that Dr. Grant has been in Winnipeg since May, 1959.

Temporarily associated with Dr. Grant, is Dr. Audrey Owens, Paediatrician, who has been assistant to Dr. Harold Popham, Medical Arts.

☆

My grape vine spies also report that in the near future Dr. Christine Curran will desert the hurly burly of General Practice for the peace and quietness (?) and security of the Certified Paediatrician. More anon. My very best good wishes to both Audrey and Chris.

In Souris, Man., the Souris Valley School Division No. 12, at its inaugural meeting, appointed Dr. L. W. Knight as Board Chairman and Staff and Curriculum Chairman. That sounds like work, Dr. Knight.

☆

Report from the Meeting of the Royal College of Physicians and Surgeons of Canada in Montreal: Dr. Lennox Bell was appointed Vice-President in Medicine, and also as member of the college council, with our old friend Dr. Wendell Macleod, now of Saskatoon. In the surgery division Dr. C. E. Corrigan represents Manitoba.

☆

In Toronto, Dr. A. E. Childe, associate professor of radiology at the University of Manitoba, was elected president of the Canadian Association of Radiologists.

☆

Dr. and Mrs. Richard M. Proctor and family visited in Winnipeg recently, in transit to Calgary where they will reside. Dr. Proctor, U. of M., has completed P.G. work at Kansas University, Lawrence, Kansas.

☆

Dr. and Mrs. John Neufeld (U. of M. '53) announce the birth of their first son, Mark Daniel, December 7, 1959, brother for Karen and Lenore, and I gather first grandson for Dr. N. J. Neufeld, Boyd Building. Dr. Neufeld, Jr., is associated with Dr. Hodgkinson in Obstetrics and Gynaecology, Henry Ford Hospital.

☆

Dr. and Mrs. Robert Cooke announce the birth of a daughter, January 8, 1960.

☆

Dr. and Mrs. F. P. Doyle, St. Anne, Man., happily announce the safe arrival of Paul Michael, January 18th, wonderful brother for Rosemary, Patricia and Elaine.

☆

Dr. and Mrs. Russell Dunlop, announce the birth of Norman John, January 6, 1960, brother for Robbie and Susan.

☆

Dr. and Mrs. A. C. Wallace welcomed Jane Elizabeth, December 31, 1959.

☆

My "Swan Song" for an indefinite length of time. To my successor, condolences.

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Deer Lodge	Clinical Luncheon (1st Monday)			11:00 Ward Rounds		
Grace		Clinical Luncheon (3rd Tuesday)	9:00 Paediatrics 9:45 Medicine 10:30 Ob. & Gyn. 11:15 Surgery	12:00 - 2:00 p.m. Weekly Seminar		
Misericordia	1. Dept. of Surgery 2. Medical Records 3. Tissue Committee 4. Dept. of Medicine	2. Clinical Luncheon 3. Dept. Obs. & Gyn. 4. Dept. Gen. Prac.	2. Interne Committee			8:30-12:30 Ward Rounds
Municipal			7:30 p.m. Review of Deaths (2nd Wednesday)			8:30 Clinical Staff Conf. and Ward Rounds
St. Boniface	11:00 Paediatric Rounds	11:00 Surgical Rounds 11:00 Obstetrical Rounds	11:00 Grand Rounds 11:00 Cardio-Pulmonary Conf. (2nd Wednesday)	3. 8:00 Orthopedic Rounds 11:00 Tumor Clinic 12:00 Clinical Luncheon (2nd & 4th Thurs.	11:00 Medical Rounds 11:00 Cardio-Pulmonary Conf. (4th Friday)	
St. Boniface Sanatorium		12:30 Clinical Luncheon (2nd Tuesday)				
Victoria		Tissue Committee (1st Tuesday)			1. Death Review 3. Clinical Luncheon 4. Active Med. Staff	
Winnipeg General		11-12:00 Medical Ward Rounds	9-10:00 Tumor Clinic 10-11:00 Surgical	12:15 Clin. Lunch. (1st & 3rd Thurs.)		
Brandon General			Medical Staff Lunch (Wed. prior to 2nd Tues. each month)			10:00-noon Clinical Drs. from S.W. Manitoba invited (Nov. to May)

Therapeutic vitamins in the "therapeutic" jar

Any severe disease process undermines the nutritional integrity of tissue.[1] To counteract physiologic stress depletion of B and C vitamins, prescribe high potency STRESSCAPS . . . in burns . . . fractures . . . severe infection . . . surgery . . . and in chronic disorders such as arthritis, alcoholism or colitis.

The attractive STRESSCAPS jar also plays an important therapeutic role . . . reminding the patient of his daily dosage . . . assuring adequate intake for full metabolic support.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average dose 1-2 capsules daily.

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Stress Formula Vitamins Lederle

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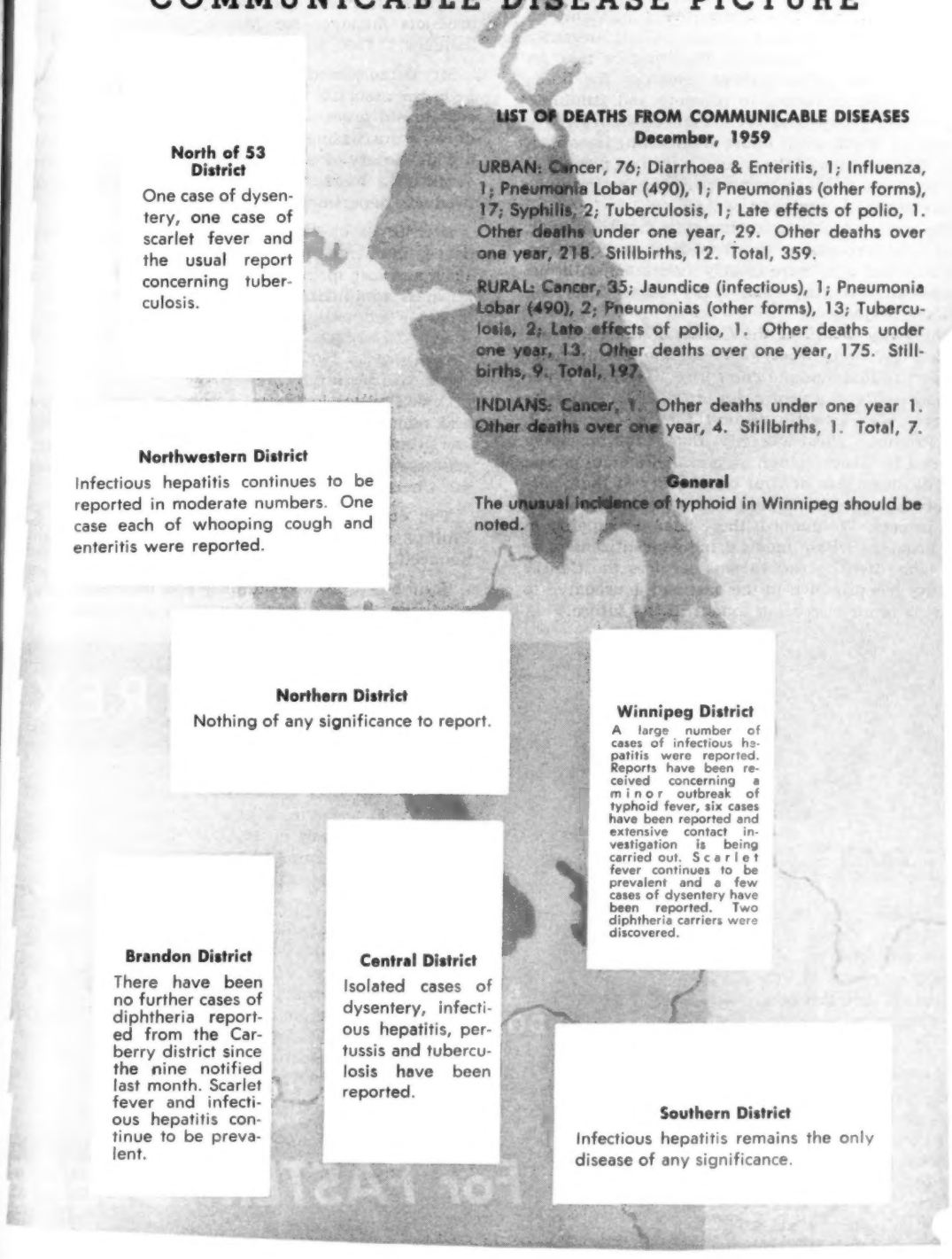
DEPARTMENT OF HEALTH & PUBLIC WELFARE

COMMUNICABLE DISEASE PICTURE



LIST OF DEATHS FROM COMMUNICABLE DISEASES
December, 1959

URBAN: Cancer, 76; Diarrhoea & Enteritis, 1; Influenza, 1; Pneumonia Lobar (490), 1; Pneumonias (other forms), 17; Syphilis, 2; Tuberculosis, 1; Late effects of polio, 1. Other deaths under one year, 29. Other deaths over one year, 218. Stillbirths, 12. Total, 359.

RURAL: Cancer, 35; Jaundice (infectious), 1; Pneumonia Lobar (490), 2; Pneumonias (other forms), 13; Tuberculosis, 2; Late effects of polio, 1. Other deaths under one year, 13. Other deaths over one year, 175. Stillbirths, 9. Total, 197.

INDIANS: Cancer, 1. Other deaths under one year 1. Other deaths over one year, 4. Stillbirths, 1. Total, 7.

General
The unusual incidence of typhoid in Winnipeg should be noted.

North of 53 District
One case of dysentery, one case of scarlet fever and the usual report concerning tuberculosis.

Northwestern District
Infectious hepatitis continues to be reported in moderate numbers. One case each of whooping cough and enteritis were reported.

Northern District
Nothing of any significance to report.

Winnipeg District
A large number of cases of infectious hepatitis were reported. Reports have been received concerning a minor outbreak of typhoid fever, six cases have been reported and extensive contact investigation is being carried out. Scarlet fever continues to be prevalent and a few cases of dysentery have been reported. Two diphtheria carriers were discovered.

Brandon District
There have been no further cases of diphtheria reported from the Carberry district since the nine notified last month. Scarlet fever and infectious hepatitis continue to be prevalent.

Central District
Isolated cases of dysentery, infectious hepatitis, pertussis and tuberculosis have been reported.

Southern District
Infectious hepatitis remains the only disease of any significance.

A Special Appeal to the Doctors of the Province

The Medical Advisory Committee of the Manitoba Division of the Canadian Cancer Society urgently requests that all Doctors of the Province take an active interest in the present campaign for funds and use their influence to promote and stimulate the welfare groups and individuals of their locality to make a worth while effort in obtaining the objective. The services of the specially trained personnel are available to all Cancer patients of the Province at the specially equipped centres.

The cancer problem, its diagnosis and treatment, is of vital importance to all medical practitioners. We feel that it is more closely associated with our professional routine than many other deserving welfare projects.

The Laity Board of the Cancer Foundation and Society give very freely of their time and financial support to this humane enterprise. Surely it is our responsibility as a profession to at least equal their efforts. We earnestly request that all doctors in the Province, rural and city alike, take an active interest in this campaign by personal donations and by advising those of your community of their personal responsibility in supporting this welfare fund and project. We doubt if there is a municipality in the province whose medical indigent citizens have not benefitted by the various services the Cancer Society has provided in the past and is prepared to provide to an increasing extent in the future.

New Appointments

Arthur J. Basso will become assistant narcotic products manager for Merck Chemical Division January 1, 1960, it was announced here today.

Mr. Basso joined Merck nine years ago, and has been an associate chemist in basic scientific research and process development in medicinal products, a purchasing agent responsible for procuring a wide variety of chemical raw materials, and more recently, a marketing specialist in the medicinal products department.

Born in Brooklyn, Mr. Basso received a master's degree in chemistry from Dusquesne University in 1950, and last spring received a master's degree in business administration from Rutgers University.

☆

O. J. Phillips has been appointed vice-president and managing director for E. R. Squibb & Sons Ltd., Canada, it was announced by G. M. Weimer, general manager, Squibb International, Olin Mathieson Chemical Corporation.

The position formerly was held by Gordon K. Phillips whose new responsibilities will be announced shortly.

Squibb is a producer of drug and pharmaceutical products with affiliates throughout the world.